AMERICAN HEART JOURNAL

September, 1960
Volume 60, No. 3

Editorial

The Problem Of Drug Dosage

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It may seem at first glance that a discussion of dosage of drugs is trite and unnecessary. However, in teaching medical students and in postgraduate work, it is found that there is a surprising amount of misinformation as to what constitutes the proper therapeutic dose of a particular drug for a particular patient at a particular time. The whole problem is much more complicated than it first appears to be. Let us first consider the answer to the simple question: What is the dose of a drug?

For each new drug there is a recommended dose. This dose is determined by the clinical trials of several investigators. The aim is to arrive at a dose which will produce the maximum therapeutic effect without undesirable or dangerous side effects. Often, the original dose must be revised up or down as the drug becomes more generally used. For instance, the originally recommended dose of reserpine of 0.25 mg. three times a day was found to produce profound mental depression, although the effect on hypertension for which the drug was given was good. Therefore, the present recommended dose is 0.1 mg. twice a day. On the other hand, the dose of pentaerythritol tetranitrate was originally set at 10.0 mg. four times a day. The dose was found to be ineffective in the majority of patients; so a tablet of 20.0 mg. to be used four times a day is also available. Even this dose is not adequate for many patients. The dose of a drug, even that of the new drugs, cannot be set as a fixed amount for every patient.

Actually, going back to basic pharmacology, there are several doses to each drug. These are: (1) *The minimal effective dose:* the smallest dose which will demonstrate some action of the drug. (2) *The therapeutic dose:* the dose required to produce the desired therapeutic effect. (3) *The maximal tolerated dose:* the largest dose that can be given without causing toxic effects. The range of dosage between the therapeutic dose and the maximal tolerated dose is the therapeutic

Received for publication Feb. 3, 1960.

range. This range is notoriously low with digitalis. The therapeutic dose for digitalis powdered leaf and most of the glycosides is about 65 per cent of the toxic dose. (4) *The toxic dose:* an acute toxic dose is easy to determine. However, long range toxicity is more difficult—such as noted above with reserpine. (5) *The fatal dose:* the fatal dose has medicolegal implications, and is one dose we all hope to avoid.

None of the aforementioned doses can be determined, especially the therapeutic dose, if the patient has an idiosyncrasy to the drug.

Dosage also depends on: (1) the mode of administration, (2) frequency of administration, (3) tolerance, and (4) electrolyte balance.

1. *Mode of Administration.*—Oral doses, because of varying difficulties in absorption from the gastrointestinal tract, are usually greater than intravenous or intramuscular doses.

2. *Frequency of Administration.*—Frequency of administration takes into account the time at which the maximal effect occurs after administration and the duration of effect. The effect of the sublingual administration of nitroglycerin is almost immediate, and the duration of effect is 5 minutes. Therefore, it is completely irrational to combine nitroglycerin in a prescription or tablet with other drugs whose duration of action may be several hours. The maximum effect of a single dose of digitoxin given orally is not reached for several hours. Therefore, in digitalizing with digitoxin, one would not give fractional doses at intervals of less than 8 hours, otherwise the total digitalizing dose will be overshot and toxicity may result.

3. *Tolerance.*—Tolerance develops to a number of drugs and this will affect the dose. The ganglionic blocking agents are an example. As these drugs are continued to be used, it is found that larger and larger doses are required to produce a therapeutic effect.

4. *Electrolyte Balance.*—A shift in electrolyte balance may affect the dose of certain drugs. An excellent example is the decrease in tolerated dosage of digitalis as the body is depleted of potassium when thiazide derivatives are used too vigorously as diuretics.

There is no fixed dose of any drug which is applicable to every patient and under every circumstance. The *U. S. Pharmacopeia* lists a "usual dose" for each drug. This is probably a better term than "average" or "mean" dose. Thus, if we take the usual maintenance dose of digoxin, for instance, as 0.5 mg. a day, we will find that an occasional patient may require as much as 1.5 mg. per day, yet other patients can tolerate only as much as 0.125 mg. per day. If one should plot the dosage curve for a larger number of patients, a typical probability curve will result.

It can be seen quite readily that the tendency on the part of drug manufacturers to combine two or more drugs in one tablet is completely irrational. One must determine for each drug the ideal therapeutic dose for each patient. Even this dose, when once determined, may require adjustment from time to time. Adjustment of dosage is impossible when two or more drugs are combined in the same tablet or capsule.

Clinical Communications

Five-Year Survival of Patients With Malignant Hypertension Treated With Antihypertensive Agents

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Franz Volhard and Theodor Fahr[1] are given credit for delineating the malignant from the benign forms of hypertension in their clinicopathologic study reported in 1914. The pathogenesis of malignant hypertension is that of a rapidly progressive disease with fatal termination, commonly ending in uremia.[1-9] It has been estimated that approximately 1 per cent of hypertensive patients develop the malignant phase.[2] Common features of the condition include severely elevated blood pressure, headache, visual disturbances, anorexia, loss of weight, weakness, and the signs and symptoms of cardiac and renal failure. The patients are most often seen during the third and fourth decades, whereas in older patients the benign forms of hypertension are commonly encountered.

In 1939, Keith, Wagener and Barker[10] divided hypertensive disease into four categories. Their distinguishing feature of Grade IV, or malignant, hypertensive patients was papilledema of the optic fundus. In their group of patients, 79 per cent were dead within 1 year of diagnosis. The 5-year survival rate was less than 1 per cent. In 1953, Schottstaedt and Sokolow,[3] in reporting on 104 patients, found that only 3 of 88 untreated patients lived longer than 2½ years. The untreated patients with adequate renal function (S.G. 1.020 or above and phenolsulfonphthalein greater than 50 per cent in 2 hours) on initial examination had an average survival period of 16.3 months as compared to the over-all mean survival of 8.4 months. In 1958, Kincaid-Smith, McMichael and Murphy[2] reported only 1 5-year survivor out of 105 untreated patients. In their series the mortality was 90 per cent at the end of 1 year.

The cardinal sign in establishing the diagnosis of malignant hypertension is the presence of papilledema. This finding may also be used as a prognostic

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Supported in part by Grant H-720 from the National Heart Institute, National Institutes of Health, and by a research grant from Irwin, Neisler & Company, Decatur, Ill.

Received for publication Jan. 8, 1960.

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guide, because with the regression of papilledema the survival rate improves. Keith and Wagener[11] found a 5-year survival of 40 per cent in 15 patients exhibiting spontaneous disappearance of papilledema. However, spontaneous regression is a rare occurrence.

Disappearance of papilledema also may occur with the reduction of blood pressure produced by antihypertensive therapy. Dustan, Schneckloth, Corcoran and Page[12] reported a 33 per cent 5-year survival in a selected series of 84 patients who received potent antihypertensive drugs. Perry and Schroeder[13] indicated a 4-year survival of 50 per cent in 82 treated patients. McMichael[14] found a 5-year life expectancy of 50 per cent in drug-treated patients who initially did not exhibit marked elevations of blood urea, whereas Smirk[15] reported a 56 per cent 4-year survival in malignant hypertensive patients. The present study summarizes the clinical and pathologic data on 64 drug-treated patients with malignant hypertension who came under observation and treatment at Mt. Alto Veterans Adminstration and Georgetown University Hospitals between the years 1949 and 1953, and reports on their follow-up to the end of 1958.

METHODS AND MATERIALS

The presence of papilledema not associated with obvious causes, such as cerebral hemorrhage or tumor, was a prerequisite for inclusion of patients in this series. Survival times were calculated from the initial observation of papilledema. In the present series there were 41 Caucasian and 23 Negro patients. Fifty-three were men and 11 were women. Their ages ranged between 23 and 61 years (mean 45.7, S.D. 10.3 years). On the basis of the needs of the individual patient and the choice of agents available at the time, the following drugs were used: various derivatives of rauwolfia, hydralazine, veratrum and its derivatives; blocking agents such as hexamethonium and pentolinium, and most recently chlorothiazide. Some patients also received chlorpromazine, phenobarbital, or meprobamate. The methods used for administering these drugs have been described elsewhere.[16-20]

RESULTS

Survival and Height of Blood Pressure.—Fourteen of 64 patients survived 5 years or longer (Fig. 1). Their ages at the time of entrance to the hospital averaged 42.3 (S.D. 9.4) years, with a range of 26 to 60 years. The average level of blood pressure prior to treatment in the group as a whole was 221/141 mm. Hg. In the patients who survived 5 years or longer, the average blood pressure before treatment was 218/140 mm. Hg. The average blood pressure after 5 years of therapy in these 14 patients was 147/99 mm. Hg. The mean of the pretreatment blood pressures in the 50 patients who did not survive for 5 years was 221/141 mm. Hg; and the mean of their last available blood pressures was 192/119 mm. Hg. The reduction of both systolic and diastolic blood pressure was significantly greater ($p < .01$) in the group who lived for 5 years than in the group who did not.

The survival rate of the Negro patients was not significantly different from that of the Caucasians; it was 54 per cent at 2 years and 20 per cent at 5 years, as compared to the 46 per cent for Caucasians at 2 years and 22 per cent at 5 years.

Funduscopic and Electrocardiographic Findings.—In 9 of the 14 patients who survived for 5 years the grade of retinopathy was recorded at or near the fifth year and found to be Grade II (Keith, Wagener and Barker classification[10])

or lower in each case. The results of electrocardiograms were available in 48 patients prior to treatment. All except 3 showed some degree of abnormality. Left ventricular hypertrophy was the most common finding. Two of the 3 patients with normal pretreatment electrocardiograms did not survive for 5 years.

Renal Function.—Pretherapy data on excretion of phenolsulfonphthalein were available in 37 patients. With 3 exceptions, all of these patients excreted less than 25 per cent of the dye in the 15-minute sample (Fig. 2). Two patients who exhibited excretions of phenolsulfonphthalein of 25 per cent or more were 5-year survivors. One is still alive 7½ years after diagnosis.

Levels of blood nitrogen as blood urea nitrogen or nonprotein nitrogen were available in 52 patients prior to therapy. They are plotted against survival time in Fig. 3. The values are elevated in the majority of cases. Three of the 14 patients who survived for 5 years had values above normal levels. However, the elevations in these 3 patients could be explained in part on the basis of congestive heart failure.

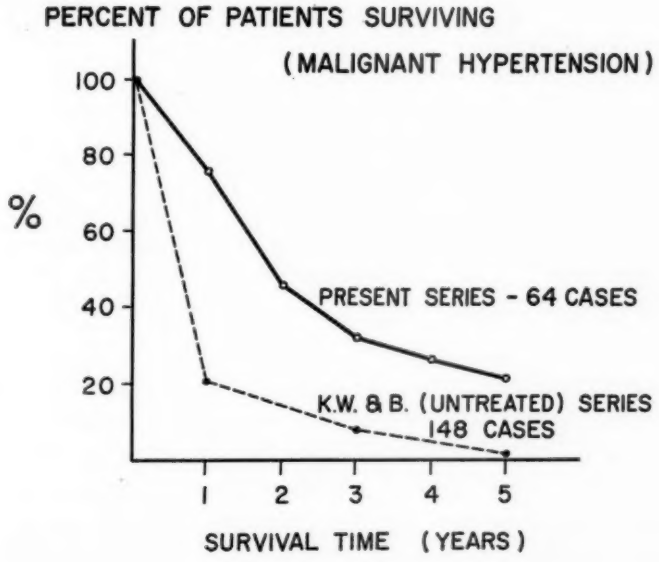

Fig. 1.—Survival times of present treated series (*solid line*) compared to the untreated series of Keith, Wagener and Barker[10] (*broken line*).

The excretion of phenolsulfonphthalein was determined prior to any treatment in 9 of the 14 patients who survived 5 years or longer. The excretion at the end of 15 minutes was 25 per cent or higher in 2 patients, 15 per cent in 4, 10 per cent in 1, 5 per cent in 1, and 2.5 per cent in 1. The blood nonprotein nitrogen was normal in all except 2 patients in whom the elevation was only moderate (44 and 58 mg. per cent, respectively) and was accompanied by clinical evidence of congestive heart failure.

Causes of Death and Autopsy Findings.—At the time of this review, 13 patients of the total of 64 were still alive. In the nonsurvivors (including 22 autopsied cases) the causes of death were diagnosed as: cerebral vascular accident in 15, cardiac complications in 12, renal in 13, pneumonia in 3, suicide in 1,

and rupture of an aneurysm of the abdominal aorta in 1. The immediate cause of death in 6 patients was not stipulated. These were cases of sudden death, and autopsy examination was not made. With the exclusion of this latter group, the most frequent fatal complications were cerebral vascular in 33 per cent, renal in 29 per cent, and cardiac in 27 per cent.

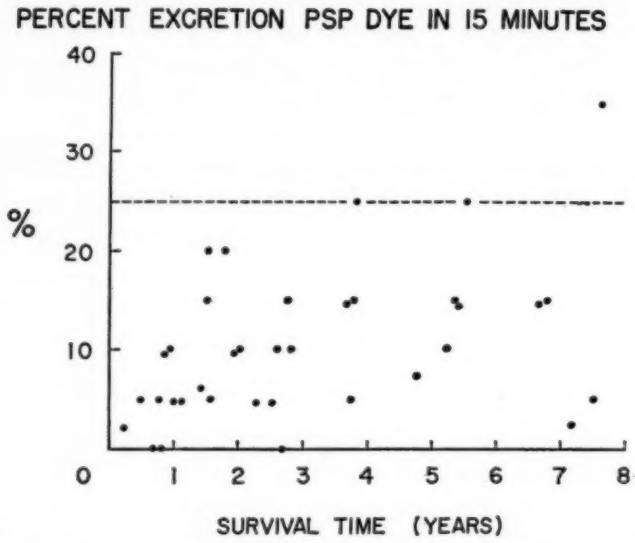

Fig. 2.—Pretreatment percentage excretions of phenolsulfonphthalein in 15-minute samples (*ordinate*) and survival times (*abscissa*). Predominance of subnormal values and lack of correlation with survival time is depicted.

In the 22 autopsied cases, 8 deaths were due primarily to renal failure, 7 to intracerebral complications, and 4 to cardiac involvement; 2 patients died of bronchopneumonia, and 1 of rupture of an abdominal aortic aneurysm. The kidneys of 5 of the 8 patients who died of uremia exhibited evidence of malignant nephrosclerosis. In the other 3, 1 showed chronic pyelonephritis, 1 chronic glomerulonephritis, and 1 severe benign nephrosclerosis. Of the 4 cardiac deaths, 2 were considered to be due to arrhythmias and 2 to myocardial infarction. In 6 patients with cerebrovascular complications the causes of death were intracranial hemorrhage (involving the pontine areas in 2 patients), whereas in 1 patient, death was thought to be due to a cerebellar pressure cone. In this patient, lumbar puncture was performed 4 days before death; during the procedure the spinal fluid pressure fell from 210 to 70 mm. of water. The blood pressure recorded on the day of the lumbar puncture was 200/138 mm. Hg. In addition to the pressure cone the autopsy disclosed an edematous brain with foci of old encephalomalacia in the cerebellum, basal ganglia, and pons, similar to the findings in cases reported previously.[21] The patient had been relatively asymptomatic under treatment with digitalis, hexamethonium, and hydralazine since a previous admission 6 months prior to the terminal event.

Atherosclerosis of the aorta and coronary and cerebral arteries was frequently observed in the 22 autopsied cases. Aortic atherosclerosis was described as being severe in 8, moderate in 9, minimal in 3, absent in 1, and was not commented

on in 1. Coronary atherosclerosis was severe in 7, moderately severe in 11, minimal in 2, absent in 1, and not described in 1. The patient who had neither aortic or coronary sclerosis was 28 years old at the time of diagnosis and died 45 months later of a pontine hemorrhage. Autopsy disclosed a relatively advanced degree of atherosclerosis in the cerebral vessels for a man of 31 years. The cerebral arteries were described in 15 cases, and moderate to marked sclerosis was seen in all 15. Included in these were 2 cases in which aneurysms of the cerebral arteries were found.

The weights of the hearts averaged 624 grams, with a range of 320 to 850 grams. The average weight of the kidneys was 133 grams (range, 70 to 200 grams). Evidence of malignant nephrosclerosis was mentioned in 13, or 59 per cent, of these patients.

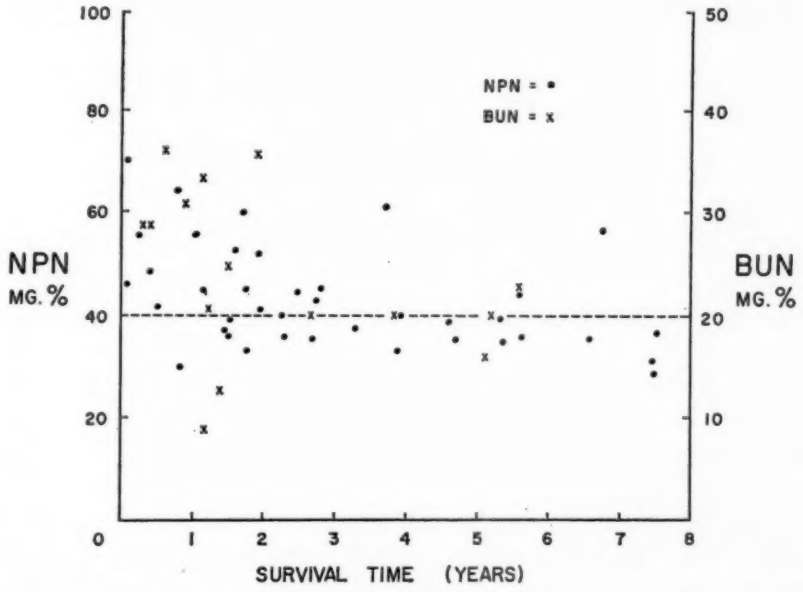

Fig. 3.—Pretreatment levels of blood urea nitrogen (*BUN*) or nonprotein nitrogen (*NPN*) (*ordinate*) compared to survival times (*abscissa*). There appears to be an approximate inverse correlation between the height of the blood urea nitrogen or nonprotein nitrogen and the survival time.

DISCUSSION

Survival time appeared to correlate significantly with the extent of renal damage prior to therapy. Thus, the majority of the patients who failed to survive for 5 years exhibited elevated values of nonprotein nitrogen. On the other hand, only 2 of the 14 patients who survived for 5 years manifested nitrogen retention, and in these 2 the uremia was moderate and associated with congestive heart failure. The survival rate was not so good in this series as that reported by others.[12-15] The reason may be that the majority of our patients had advanced renal damage at the time therapy was initiated.

Antihypertensive drug therapy seemed to change the frequency distribution of fatal complications. In the untreated series of Kincaid-Smith, McMichael and Murphy,[2] only 20 per cent died of cerebral vascular accidents, and 14 per

cent of cardiac complications; death in the remainder was due primarily to renal failure. By contrast, in the present treated series, 33 per cent of the deaths were due to cerebrovascular accidents, 27 to heart disease, and only 29 per cent to renal failure. Atherosclerosis, particularly of the cerebral vessels, also was extremely common in the treated cases. As has been pointed out by Dustan and associates,[12] premature atherosclerosis and the complications therefrom become prominent features in the patients with malignant hypertension whose lives are prolonged by antihypertensive drug treatment.

There was a significant difference in the extent of reduction of blood pressure in the patients who survived for 5 years and in those who did not; the average reduction was greater in the survivors. This result suggests that survival is related directly to the extent of reduction of blood pressure. If this is true, survival may be further improved with the development of more effective therapy. It should be pointed out, however, that, in general, the patients with less advanced vascular damage appeared to be more responsive to antihypertensive drugs. Thus, the survivors may represent the group who have not yet reached the stage of irreversible organic changes, particularly renal vascular damage. This would place a ceiling on the number of possible survivors, no matter how effective antihypertensive therapy becomes. A further reasonable assumption, on the basis of current evidence, is that a vigorous attack on the elevation of blood pressure should be made at the first sign of malignant hypertension, or better still, before the malignant phase develops.

A surprising result of this study was that the Negro patients lived almost as long as the Caucasians while under treatment. It should be pointed out, however, that there were many Negro patients with malignant hypertension who were not included in this analysis because they entered the hospital in stages of renal failure so advanced as to preclude antihypertensive therapy. Moreover, the Negro patients included in this study were the more "cooperative" patients who attended the follow-up clinic regularly and presumably were adhering to the prescribed therapeutic regimen. Although the series is small, the present results suggest that if the Negro receives and maintains adequate treatment before the stage of irreversible organic damage, he can survive as long as the Caucasian patient.

SUMMARY AND CONCLUSIONS

The case histories of 64 patients who were treated for malignant hypertension were reviewed with the purpose of determining the influence of antihypertensive drug therapy on the course of their disease. As compared to reports of survival in untreated series, the survival rate was significantly improved. The group surviving for 5 years or longer was characterized by normal or nearly normal levels of nonprotein nitrogen prior to treatment, and by significantly greater reductions of both systolic and diastolic blood pressure after treatment, as compared to the nonsurviving group. The Negro patients who received and maintained adequate treatment, and who came under observation before the advent of irreversible renal failure, survived, on the average, for as long a period as the Caucasians.

Extensive atherosclerosis, particularly of the cerebral arteries, was a consistent feature in the autopsied patients. In addition, cerebral vascular accidents and myocardial infarction were more frequent fatal complications than in untreated cases. These findings confirm the previous report of Dustan and coworkers[12] that atherosclerosis and the complications arising therefrom become prominent when the lives of these patients are prolonged by treatment.

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A Study at Autopsy of the Relation of Absence of the Q Wave in Leads I, aV_L, V_5, and V_6 to Septal Fibrosis

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An electrocardiographic syndrome found in septal fibrosis was described in 1956, which consisted of absent Q waves in Leads I, V_5, and V_6.[1] The present report is a more detailed evaluation of septal fibrosis based on a study of 142 autopsies with electrocardiographic correlations.

MATERIALS AND METHODS

The hearts of 1,184 consecutive autopsies for the last 4 years were studied at the Veterans Administration Hospital in New Orleans. In addition to the usual postmortem examination, the interventricular septum was carefully examined for areas of fibrosis. Such areas of fibrosis were revealed best by making several cuts through the septum parallel with the two endocardial surfaces. The postmortem findings were correlated with the 12-lead electrocardiogram (ECG), especially for the absolute absence of Q waves in Leads I, aV_L, V_5, and V_6.

RESULTS

The results are summarized in Fig. 1 and Tables I and II.

Of the 1,184 hearts examined, 142 (12 per cent) showed evidence of septal fibrosis at necropsy. All of the patients with septal fibrosis were men (because of the nature of the hospital). Their ages ranged from 38 to 84 years; the mean age was 63 years. Ninety-seven were white and 45 were Negro.

Of 142 patients, 3 had left bundle branch block and 6 had right bundle branch block. Since the presence or absence of a Q wave in precordial leads recorded from the left side of the transition zone is difficult to interpret in the presence of bundle branch block, the data from the 9 patients with bundle branch block were eliminated. In addition, there were no electrocardiograms for 6 other patients whose hearts showed septal fibrosis at autopsy. For the remaining 127 patients, however, at least one ECG was available.

The electrocardiogram in 101 (80 per cent) of the 127 patients with septal fibrosis demonstrated an absence of Q waves in Leads I, aV_L, V_5, and V_6. In the remaining 26 patients (20 per cent), Q waves were present in these leads despite

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Supported by grants from the U. S. Public Health Service.

Received for publication Jan. 8, 1960.

the existence of septal fibrosis (Table I). Of the 1,184 patients autopsied, 27 (2 per cent) had an absence of Q waves in Leads I, aV_L, V_5, and V_6, even though no areas of fibrosis were found in the septum.

Left ventricular hypertrophy was present at autopsy in 114 (80 per cent) of the 142 patients with septal fibrosis. In 118 (83 per cent) of these patients, a definite history of angina pectoris was obtained; in 15 patients (11 per cent), angina pectoris was not evident clinically; and in 9 patients (6 per cent) the history was too indefinite for determination of whether or not angina pectoris was present.

TABLE I. CORRELATION BETWEEN ELECTROCARDIOGRAPHIC AND AUTOPSY FINDINGS

AUTOPSIES	SEPTAL FIBROSIS AT AUTOPSY	PATIENTS INCLUDED IN STUDY*	ECG EVIDENCE OF SEPTAL FIBROSIS	SEPTAL FIBROSIS WITHOUT ECG EVIDENCE
1,184	142 (12%)	127	101 (80%)	26 (20%)

*Nine patients were eliminated because of bundle branch block, and 6 because no electrocardiograms were available.

TABLE II. CLINICAL FINDINGS IN THE 142 PATIENTS WITH SEPTAL FIBROSIS

CLINICAL FINDINGS	NUMBER OF PATIENTS	PER CENT
Angina	118	83
LVH	114	80

DISCUSSION

Recently, the concepts of Lewis[2] concerning the spread of electrical activation through the interventricular septum have been challenged,[3,4] and the hypothesis that the septum is excited equally from both sides or that the base of the septum is the first portion of that structure to be activated is generally no longer accepted. The mid-portion of the left side of the interventricular septum is probably activated first (0.000 to 0.010 second), resulting in a vectorial force which progresses through the left septal muscle mass and produces initial negative QRS deflections (septal Q wave) in Lead I and in unipolar leads recorded from points on the body to the left of the interventricular septum. Following early septal activation, electrical forces are developed in the free wall of the left ventricle probably *before* activation of the right ventricular muscle mass takes place. These forces are directed to the left,[5] resulting in positive deflections (R waves) in the same leads.

When fibrosis is present, septal muscle is replaced by electrically inactive fibrous tissue, and the muscle surrounding these areas of fibrosis is probably injured also. Under these circumstances, early activation of the septum cannot take place. Instead, the left ventricular muscle mass is probably initially activated

in the region of the apex. This results in an early vectorial force (0.010 to 0.015 second) which is directed to the left so that an initial positive QRS deflection is displayed in leads recorded from points on the body to the left of the septum (Fig. 1). In 114 (80 per cent) of the patients included in this study who were found to have areas of fibrosis in the septum at necropsy, there were no Q waves in Leads I, aV_L, V_5, and V_6.

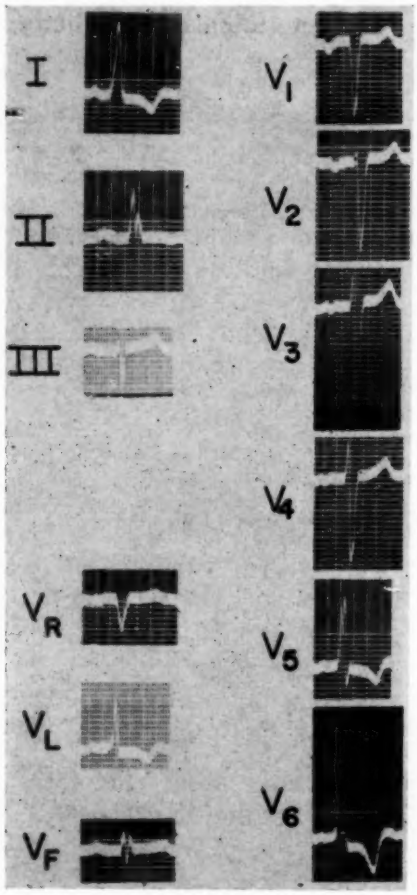

Fig. 1.—Typical electrocardiogram of a patient with septal fibrosis. Patient No. 52. Heart weight, 532 grams.

Unusual degrees of cardiac rotation must be considered when septal Q waves are absent. Of the 142 patients with septal fibrosis, 114 (80 per cent) also had left ventricular hypertrophy (LVH). Since the counterclockwise rotation of the heart associated with LVH would tend to preserve the septal Q wave, the association of left ventricular hypertrophy in the absence of septal Q waves strengthens the evidence for septal fibrosis.

Despite the presence of septal fibrosis, Q waves were displayed in Leads I, aV_L, V_5, and V_6 in 26 patients. In 14 of these patients there was massive left ventricular hypertrophy. It is conceivable that in these instances the septal hypertrophy overshadowed the fibrosis so that septal Q waves were produced.

Furthermore, the areas of fibrosis were patchy, so that sufficient uninvolved areas of muscle may have remained to be depolarized early in the electrical cycle to produce septal Q waves.

The supply of blood to the septum is derived from penetrating branches of the left anterior descending and right posterior descending coronary arteries, with the former supplying the major portion of the septum.[6] Occlusion of one or more of these penetrating branches is probably responsible for the septal fibrosis. Such occlusion may occur with or without disease in the major coronary arteries. However, the high incidence of angina pectoris in the patients of this study suggests the presence of diffuse myocardial disease. Of the 142 patients with septal fibrosis, 68 (48 per cent) were found to have narrowed coronary arteries and scars in other areas of the myocardium in addition to the septum, without occlusion of the coronary arteries. Fifty-eight patients (41 per cent) had occlusive coronary artery disease, usually involving the left anterior descending coronary artery. Sixteen patients (11 per cent) had scarring in the septum but little or no scarring in other areas of the heart, and all but one had arteriosclerosis of the coronary arteries. The mechanism of the septal fibrosis in patients with prolonged periods of angina pectoris is obscure, but it may be due to spasm of one of the penetrating septal arteries, with progressive myocardial injury and accumulation of small scars.

Sodi-Pallares[7] considered electrocardiograms in which there was an absence of or "embryonic" Q waves in Leads I, aV_L, V_5, and V_6, with slurring of the initial portion of the R waves in these same leads, to represent first-degree incomplete left bundle branch block. Since no autopsy data were available, it is not known whether any of his patients had septal fibrosis, but most of the patients had clinical evidence of cardiac disease. In the present study no attempt was made to section the bundle branch.

Problems regarding this electrocardiographic and pathologic syndrome described for septal fibrosis need further investigation. For example, it has been assumed that when interventricular septal fibrosis exists, the septum is activated later than the free wall of the left ventricle. More extensive electrocardiographic studies, with anatomic and physiologic correlations, are necessary in order to establish the sequence of ventricular activation in the normal and scarred septum. The time courses of depolarization and repolarization of the myocardium of man with and without heart disease are among the most important unsettled electrophysiologic phenomena in the field of electrocardiography.

SUMMARY

In patients with an absolute absence of Q waves in Leads I, aV_L, V_5, and V_6 there is an 80 per cent possibility that septal fibrosis is present. If left ventricular hypertrophy is present and there are diminutive Q waves in these leads, septal fibrosis may be present; however, it is not possible to be certain of this. Twenty per cent of the patients without septal Q waves did not have septal fibrosis at autopsy. Most of the patients studied who had an absence of Q waves in Leads I, aV_L, V_5, and V_6 and septal fibrosis at necropsy, also had left ventricular hypertrophy and a prolonged period of angina pectoris.

We wish to express our sincere appreciation to Dr. Joseph Ziskind, Director, Department of Pathology, New Orleans Veterans Administration Hospital, for his interest and cooperation in this study.

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The Low Incidence of Myocardial Infarction in Patients With Portal Cirrhosis of the Liver: A Review of 639 Cases of Cirrhosis of the Liver From 17,731 Autopsies

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The apparent paucity of atherosclerosis in cases of chronic alcoholism[1-3] and portal cirrhosis of the liver[4] has been frequently commented upon, but, as pointed out by Cowdry,[5] controlled analyses have been lacking. The recorded incidence of myocardial infarction in cases of cirrhosis of the liver, perhaps a reliable index of the sparing effect of alcohol and/or cirrhosis upon the extent and degree of coronary sclerosis, has, for the most part, favored this view but has received scant attention. Chase and co-workers,[6] in analyzing the cause of death of 63 patients with cirrhosis, failed to mention myocardial infarction. Pollard and co-authors,[7] in reviewing extrahepatic complications of cirrhosis in 201 clinical cases (24 with biopsy and 31 with autopsy), reported that only 3 had myocardial infarction and commented that in only one of these was the cirrhosis severe. MacDonald and Mallory[8] found 6 myocardial infarcts (4 recent and 2 healed) in 221 autopsies (2.7 per cent) performed on subjects who had postnecrotic cirrhosis. Because of the over-all incidence of infarction (10.3 per cent), they stated: "It would appear that patients with postnecrotic cirrhosis have a lower incidence of myocardial infarction than the general autopsy population." Lunseth and associates,[9] on the other hand, in a study of heart disease in 180 hospitalized patients dying of portal cirrhosis, found myocardial infarction in 11 of 108 autopsied cases. No mention was made as to whether the infarcts were recent or healed.

Recent interest in the "thrombotic theory" of the pathogenesis of atherosclerosis, coupled with reports that the blood of patients with cirrhosis exhibits enhanced fibrolytic activity[10-15] as well as alteration in coagulation factors,[15,16] led to the present study.

This study was supported in part by grants from the James F. Mitchell Foundation and the Washington Heart Association, and United States Public Health Service Grant No. H-4166.

Received for publication Jan. 25, 1960.

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MATERIAL AND CRITERIA

Available for study in 1957 were 17,731 autopsy reports and clinical records from the diagnostic files of the Armed Forces Institute of Pathology. Analyses have shown that approximately 90 per cent of such records coming to the Armed Forces Institute of Pathology are from personnel on active duty or veterans, and 10 per cent from civilians or civilian dependents. The sample under study was made up of 96 per cent men. Eighty-four per cent were Caucasian, 15 per cent were Negro, and 1 per cent was Orientals and American Indians. The mean age was 63 years. The group also differed from the general population in that all Service personnel in the group had, upon entrance to the Service, undergone complete physical examination, and at that time presumably had neither diabetes mellitus nor arterial hypertension.

In selecting the cirrhotic group, only those having an anatomic diagnosis of portal cirrhosis, Laennec's cirrhosis, or postnecrotic cirrhosis were chosen. Those having anatomic diagnoses of obstructive jaundice, biliary cirrhosis, bile stasis, hemosiderosis, posthepatic scarring, or cardiac cirrhosis were omitted.

Only those having a specific anatomic diagnosis of myocardial infarction with substantiating gross and microscopic findings were included in the infarction group. Cases carrying anatomic diagnoses of myocardial fibrosis, focal fibrosis, thrombotic occlusion of coronary artery, or arteriosclerotic occlusion of coronary artery, but not otherwise qualified, were omitted. Microscopic evidence of myonecrosis plus cellular infiltration was the basis for the diagnosis of recent infarction.

The presence or absence of a clinical diagnosis of diabetes mellitus was noted.

RESULTS

Of the 17,731 patients autopsied, 639 were found to have anatomic diagnoses of portal cirrhosis, Laennec's cirrhosis, or postnecrotic cirrhosis. Of the 639 cirrhotic patients, 32 (4.9 per cent) were found to have myocardial infarcts. The incidence of myocardial infarction in the remaining noncirrhotic group, on the basis of examination of a random 5 per cent sample from the 17,731 autopsies in 1957, was 20.2 per cent. Hence, in the group studied, myocardial infarction was less than one fourth as common in cirrhotic patients as in noncirrhotic patients.

Of 24 diabetic patients found among the cirrhotic group, only one had myocardial infarction. (The median age of this group was 63 years).

Incidence of Recent Infarction.—Of the 32 infarcts discovered among the cirrhotic group, 12 were recent (incidence 1.8 per cent as compared to an incidence of 10 per cent in the control group). Hence, recent infarction in the group studied was one sixth as common in cirrhotic patients as in noncirrhotic patients.

Statistical analysis proved the findings to be highly significant even though the median age of the cirrhotic group was 58 years as compared to that of 63 years for the noncirrhotic group.

DISCUSSION

Whether or not factors operative in Laennec's cirrhosis suppress the incidence of myocardial infarction by virtue of a reduction in the degree and extent of coronary sclerosis, by alteration of the coagulation-fibrinolytic balance, or by other means has yet to be elucidated. The more profound effect upon the incidence of recent infarction suggests a critical mechanism which involves either clot formation or clot lysis. Alteration of coagulation factors, although occurring in cirrhosis, is insufficient in magnitude and duration (in the light of present knowledge) to account for this change. Clot lysis (fibrinolysis), on the

other hand, early noted in cirrhosis by Goodpasture,[10] and repeatedly confirmed,[11-14] may be both significant and prolonged. In light of enzymatic studies of Astrup,[17,18] such active fibrinolysis would be expected to lead to a reduction in the extent and degree of fibrin clot deposition, supporting the "thrombotic theory" of the pathogenesis of atherosclerosis as proposed years ago by Rokitansky[19] and revived by Duguid.[20] It is the belief of Astrup[17,18] that fibrin clot formation and clot lysis are continuous processes, and that imbalance of the system leads to increased fibrin deposition upon intimal surfaces of arteries, followed by tissue repair (atherosclerosis). Rapid turnover rates of fibrinogen favor this view.[21] Fibrinolysis, active at birth,[22,23] may diminish with age unless activated by shock,[24] fever,[25] or by mechanisms not yet explained in cirrhosis of the liver. Observations in recent years which correlate high-fat diets with the prevalence of atherosclerosis do not detract from this theory, since hyperlipemia has been shown to favor coagulation[26] in vivo.

CONCLUSIONS

In this study, old and/or recent myocardial infarction was found to be less than one fourth as common in cirrhotic patients as in noncirrhotic patients. This trend obtained even in the presence of diabetes mellitus.

Recent infarction was found to be one sixth as common in cirrhotic patients as in noncirrhotic patients.

The implied significance of these findings is discussed.

I am indebted to Mrs. Mardelle Reynolds, of the Armed Forces Institute of Pathology, and Ross L. Gauld, M.D., Director of the Division of Preventive Medicine, W.R.A. Institute of Research, for their assistance in compilation and analyses of statistical data.

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Candida Endocarditis. Two New Cases, With a Review of Twelve Cases Previously Reported

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Fungal endocarditis is a comparatively rare disease as shown by the fact that only 35 documented cases have been reported.[1,14] Of these, 12 were due to a species of Candida.[1-14] Six additional cases of possible Candida endocarditis have been reported but these are not well documented.[15-20] In addition, Wikler and coauthors[4] mention that 3 cases of Candida endocarditis occurring in drug addicts have been reported to them by personal communications from other physicians.[21,22]

A majority of the reported cases of fungal endocarditis have occurred since 1950, which supports the impression that there has been an increase in the overall incidence of secondary fungus infections in recent years.[7,23-31] Most secondary fungus infections are due to Candida, Aspergillus, and Mucor and occur most often in patients with chronic and debilitating diseases who have been treated with antibiotics and steroids. Widespread systemic involvement is frequently present, especially in Candida infections.

This article records the clinical and morphologic details of 2 cases of Candida endocarditis and reviews the findings on previously reported cases. One of our patients had a pre-existing subacute bacterial endocarditis which was due to enterococcus, and he had been on prolonged antibiotic therapy. Our second patient had rheumatic fever and was given a long course of antibiotic and steroid therapy. This case is of special interest because the diagnosis was made during life and the patient was treated with amphotericin B.

CASE REPORTS

CASE 1.—J. C., a 38-year-old Negro man, was admitted to Charity Hospital of Louisiana at New Orleans on Oct. 10, 1953, with a perirectal abscess of 2-week duration. Past history revealed

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Supported in part by a training grant (CRT 5025) from The National Cancer Institute, U. S. Public Health Service.

Received for publication Jan. 6, 1960.

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that in 1949 he also had a perirectal abscess which was drained. At that time he was found to have valvular heart disease without history of rheumatic fever or signs and symptoms of congestive heart failure. He was not seen again until the present admission.

Physical examination revealed a blood pressure of 120/56 mm. Hg. Except for the perirectal abscess, abnormal findings were limited to the heart, which was enlarged. Mitral and aortic systolic and diastolic murmurs were present.

Laboratory work revealed a hemoglobin of 10 Gm. per cent, hematocrit of 35 per cent, and a white blood cell count of 14,800 with a normal differential. Blood chemistries, urinalysis, and a serologic test for syphilis were normal. Blood for culture was taken but not reported upon during this hospital stay.

The perirectal abscess was incised and drained and the patient was treated with penicillin and streptomycin. He was discharged after 3 days but was readmitted 1 week later with a history of anorexia, weakness, fever, and night sweats since his discharge. He appeared acutely ill and had a temperature of 100°F. The heart was enlarged as before but the murmurs were louder and harsher. In addition, an apical gallop rhythm was present, as well as peripheral signs of aortic valvular insufficiency. The electrocardiogram showed a sinus tachycardia with slightly elevated S-T segments in Leads V_{4-6}. Laboratory work revealed anemia and leukocytosis. It was now learned that alpha hemolytic streptococci had been isolated from the blood culture made during the previous admission. Enterococcus was recovered from all of seven blood cultures made during the next 2 days, and a diagnosis of enterococcus endocarditis was made.

Fig. 1.—Case 1. Aortic valve showing vegetations. Cusps are thickened and ulcerated.

The patient was treated with penicillin intravenously in doses ranging from 15 to 45 million units per day for 8 weeks. Two grams of streptomycin per day was given concomitantly for 6 weeks, followed by erythromycin, 2.4 Gm. per day, for 4 weeks. During this time all blood cultures were negative. However, several serious complications occurred. A urethritis and partial urethral stricture developed, and urine cultures became positive for *Aerobacter aerogenes*. A thrombophlebitis developed at the sites of intravenous infusions and in the right calf, but this resolved after treatment with heparin. The perirectal abscess recurred and was again incised and drained. At the termination of antibiotic therapy the patient was afebrile and blood cultures were negative.

On Dec. 28, 1953, the patient complained of shortness of breath, and râles were heard at both lung bases. One week later small miliary abscesses appeared over the skin of the trunk, and *Candida albicans* was recovered on culture of these lesions. The heart murmurs became louder,

and a chest x-ray film revealed a further increase in the size of the heart, increased vascular markings, and a small right pleural effusion. Administration of penicillin, streptomycin, and erythromycin was resumed even though cultures of blood and pleural fluid remained negative. During January, 1954, the congestive heart failure became worse and the patient underwent digitalization. Seven blood cultures made in January were negative. On Jan. 27, 1954, a tender swollen area appeared over the sternum. The following day small petechiae were observed on the sole of the right foot, and tender nodules developed on the big toe of the right foot and palm of the left hand. On February 1, Candida (species not identified) grew out on blood culture, but this finding was discounted at the time as a probable contaminant. The patient's condition continued to deteriorate and he developed nausea, vomiting, and pains in the right upper quadrant and epigastrium. These symptoms were thought to be due to septic emboli caused by an exacerbation of the enterococcus endocarditis. Eighteen blood cultures made in February were negative. The patient died in congestive heart failure on Feb. 20, 1954, 4 months after admission.

Autopsy Findings.—The heart weighed 450 grams. Both ventricles were dilated and hypertrophied. The tricuspid and mitral valves showed some thickening of the leaflets with shortening of the chordae tendineae. The aortic valve cusps were thickened, calcified, and ulcerated. Fungating vegetations were adherent in the regions of ulceration (Fig. 1). Microscopic examination revealed a thickened, calcified cusp with a vegetation which contained filamentous and yeast forms of Candida (Fig. 2). Other histologic findings were chronic passive congestion of the lungs, centrolobular congestion and necrosis of the liver, and acute enterocolitis.

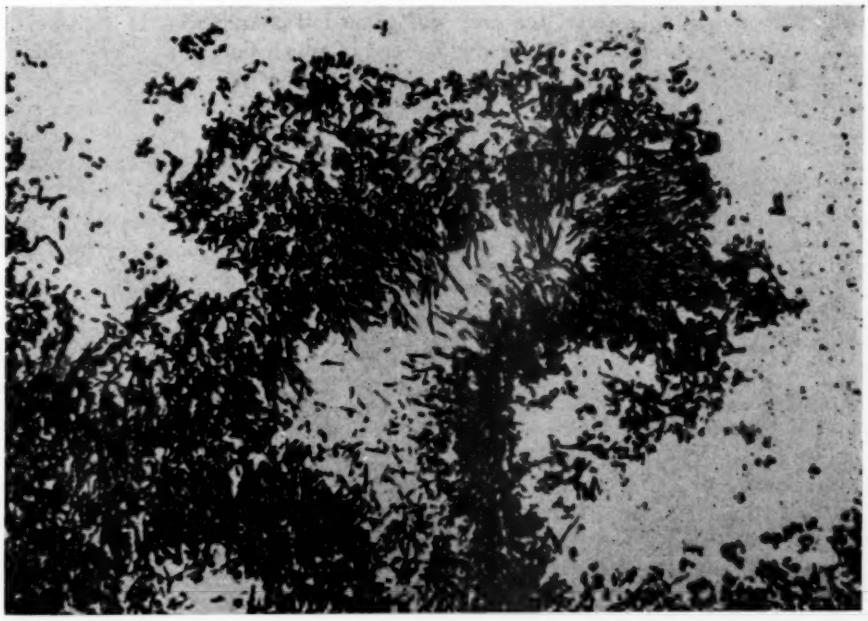

Fig. 2.—Case 1. Microscopic section of vegetation showing filamentous and yeast forms of Candida (PAS stain, magnification ×175).

CASE 2.—S. G., a 9-year-old Negro boy, entered another hospital on May 1, 1957, with a 3-month history of exertional dyspnea, puffy eyes, grunting respirations, and palpitations. Episodes of arthralgia had occurred 1 and 3 years prior to admission. Physical examination revealed a blood pressure of 90/60 mm. Hg, pulse of 120 per minute, respirations of 60 per minute, and a temperature of 100°F. The heart was enlarged to the anterior axillary line. Apical systolic and diastolic thrills and loud systolic and diastolic murmurs were present. The liver and spleen were enlarged. The antistreptolysin titer was 1:400. An electrocardiogram showed a prolonged P-R interval. The clinical diagnosis was active rheumatic carditis and congestive heart failure. The child was placed

on bed rest and was treated with digitalis and mercurial diuretics. He was subsequently given prednisone, 60 mg. per day. Because of the possibility of a concomitant subacute bacterial endocarditis he was also given 5 million units of penicillin and 2 Gm. of streptomycin per day. After 12 days of treatment he became afebrile and the prednisone was discontinued, only to be resumed 1 week later when the temperature again became elevated, ranging from 101° to 105°F. At this time he was in severe congestive heart failure. Funduscopic findings were compatible with retinal emboli. Blood cultures made at this time were reported as positive for *Candida albicans.*

The patient was transferred to Charity Hospital of Louisiana at New Orleans on June 2, 1957, where physical examination revealed retinal emboli, petechiae on the soft palate, distention of neck veins, râles in both lungs, hepatosplenomegaly, and ascites. The heart was enlarged and a loud high-pitched apical systolic murmur, a blowing apical diastolic murmur, and a rough blowing basilar systolic murmur were heard. Laboratory work revealed a hemoglobin of 9 Gm. per cent, hematocrit of 32 per cent, and red blood cell count of 3.2 million per cubic millimeter. The urine showed slight proteinuria. An electrocardiogram was compatible with left ventricular hypertrophy. After blood was obtained for culture, the patient was started on 60 mg. of prednisone, 8 million units of penicillin, and 2 Gm. of chloramphenicol per day. During the next 3 days *Candida albicans* grew out in all of fourteen blood cultures. Abscesses, from which *Candida albicans* was cultured, developed at the site of previous intravenous infusions, and these were incised and drained. On June 9, 1957, a diagnosis of probable Candida endocarditis was made and treatment with amphotericin B was instituted on the following schedule: 5 mg. per day intravenously for 4 days, 7 mg. per day for 4 days, 10 mg. per day for 4 days, and then 12 mg. per day for 8 days. After this, because the patient had poor veins, the drug was given intramuscularly, 15 mg. per day for 7 days, and then 20 mg. per day for 43 days, at the end of which time the patient died. The total duration of therapy with this drug was 70 days. During this period, prednisone, 60 mg. per day, had been continued until June 11, 1957. The dosage was reduced to 35 mg. per day on August 6, and continued at this level until August 12. With therapy, the patient gradually became afebrile, and all blood cultures after June 10 were negative. However, his general condition remained poor throughout the period of hospitalization. His cardiac status grew progressively worse, and congestive heart failure persisted despite all therapeutic measures. It was believed that the main difficulty was mitral valvular insufficiency rather than the active rheumatic process. Because of his rapidly deteriorating condition he underwent an operation on Aug. 12, 1957, at which time an attempt was made to relieve the mitral insufficiency by passing a suture around the mitral valve ring. During the procedure, cardiac arrest occurred, efforts at resuscitation failed, and the patient died.

Autopsy Findings.—The heart weighed 340 grams. Myocardial hypertrophy and dilatation of all chambers was present. The tricuspid valve showed thickened, slightly nodular areas along the leaflet margins. The left atrial endocardium was thickened, and pink fibrinous material was adherent to its surface in the region just above the mitral valve ring. The leaflets were thickened (Fig. 3). A 4 by 4 mm. firm vegetation was adherent to the posterior mitral leaflet. A 3 by 2 mm. verrucose mass attached to the chordae tendineae below the mitral valve was also present. *Candida albicans* was recovered on culture of this vegetation. The chordae tendineae of the mitral valve were thickened, shortened, and inserted on the free edges of the leaflets. The posterior leaflet was retracted. The aortic valve appeared to be normal except for some fibrinous deposits along the margins of the cusps. The coronary vessels were normal. The myocardium was flabby.

Microscopically, there was fibrous thickening of the atrial endocardium, with a fibrinous deposit on its surface. The mitral valve ring was thickened and infiltrated by neutrophils, lymphocytes, and macrophages, with some areas of necrosis. Periodic acid-Schiff stain demonstrated a small focal collection of yeast-like and filamentous organisms resembling Candida deeply buried within the valve ring (Fig. 4). The mitral valve was thickened, fibrotic, vascularized, and contained collections of lymphocytes. Sections of the vegetation revealed a fibrin meshwork, deposits of calcium, inflammatory cells, and numerous Candida. The aortic and tricuspid valves showed changes compatible with rheumatic involvement, but no Aschoff bodies were found in the myocardium. Other histologic findings were chronic passive congestion of the lungs, liver, and spleen. The left kidney contained a large healed infarct, but no organisms were found in the area.

Fig. 3.—Case 2. Mitral valve with thickened cusps and chordae tendineae.

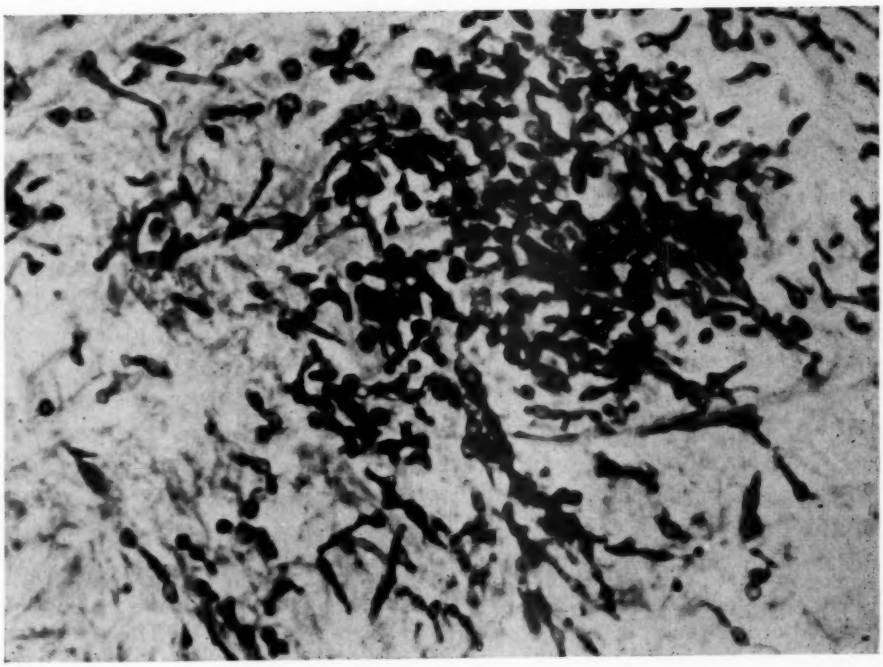

Fig. 4.—Case 2. Filamentous and yeast form of Candida in area of valve ring (PAS stain, magnification ×590).

DISCUSSION

Review of these 2 cases suggests that the occurrence of Candida infection in each instance may have been favored by the presence of a pre-existing debilitating illness and also by the therapeutic agents used. The first patient had

an enterococcus endocarditis superimposed on a previously damaged aortic valve. The debilitating effects of the primary illness, the numerous complications, and the extensive antibiotic therapy rendered the patient more vulnerable to the Candida infection. The second patient had rheumatic fever and developed Candida endocarditis during hospitalization while he was undergoing intensive treatment with antibiotics and steroids.

Recent reports have emphasized the increasing incidence of secondary infections by so-called "saprophytic" fungi in debilitated patients, after treatment with antibiotics and steroids.[23-31] These infections most commonly develop in patients who are already chronically ill with disorders such as blood dyscrasias, malignant neoplasms, diabetes mellitus, and cardiovascular disease. These observations suggest that the treatment of such patients with antibiotics and steroids increases the hazard of serious or fatal secondary fungus infection.

Review of our cases, together with those previously reported, shows that Candida endocarditis presents a clinical picture that is indistinguishable except by means of blood culture from that of subacute bacterial endocarditis. The presenting manifestations, physical findings, associated diseases, complications, and pathologic findings in the documented cases of Candida endocarditis are summarized in Table I.

The most frequent presenting manifestation was fever. However, abdominal pains and symptoms due to embolic phenomena were also common. Heart murmurs were present in 11 of the 14 patients. Petechiae and hepatosplenomegaly were also common, but Osler's nodes and clubbing of the fingers were seen in only 4 and 2 patients, respectively. Previous valvular damage was present in 11 patients, with rheumatic heart disease definitely present in 5 and probable in 4. Two patients had previous subacute bacterial endocarditis, including our patient J. C. Addiction to narcotics was present in 4 patients. The introduction of microorganisms during injection of narcotics has also been cited as the probable route of infection in a number of cases of bacterial endocarditis in drug addicts.[18] The major complications of Candida endocarditis were attributable to emboli and congestive heart failure. Unusually large vegetations were often present, and this may explain the frequency of embolic complications. Positive cultures, with five different species of Candida, were obtained in 13 patients during life or at autopsy. *Candida albicans* was the most common, being recovered in 5 of the patients. At autopsy, vegetations were present on the mitral valve in 7 patients, and on the aortic valve in 4, and combined involvement was found in 2 patients. Right-sided endocarditis was present in only 1 patient. However, in 2 patients there was a perforation from the region of the aortic valve into the right atrium.

Antifungal agents such as amphotericin B appear to offer some hope of effective treatment in some cases of systemic fungus infections.[32] In our second patient, amphotericin B was used for the Candida endocarditis, and clinically it appeared to have been effective in checking the Candida infection for a time, although it did not completely eradicate the infection. Pathologically, the vegetations in this case were small in comparison with luxuriant vegetations frequently described in most cases of untreated fungus endocarditis.

TABLE I. CLINICAL AND PATHOLOGIC DATA IN FOURTEEN CASES OF CANDIDA ENDOCARDITIS

DATA	NUMBER OF PATIENTS
Presenting Manifestations:	
Fever	11
Abdominal pains	6
Embolic phenomena	5
Congestive heart failure	4
Malaise and anorexia	4
Chest pain	3
Neurological abnormalities	2
Physical Findings:	
Fever	14
Cardiac murmurs	11
Petechiae	11
Hepatomegaly	9
Splenomegaly	7
Osler's nodes	4
Neurological abnormalities	4
Abdominal tenderness	4
Clubbing of fingers	2
Underlying Diseases:	
Rheumatic heart disease	5
Probable rheumatic heart disease	4
Addiction to narcotics	4
Previous subacute bacterial endocarditis	2
Peptic ulcer	2
Diabetes mellitus, hypertension, pulmonary disease, and rheumatoid arthritis	1 each
Major Clinical Complications:	
Embolic phenomena	9
Central nervous system (6); intestines (3); lower extremities (3); spleen (3); kidneys (2)	
Congestive heart failure	4
Renal failure	2
Meningitis and perforated bowel	1 each
Culture Identification:	
Candida albicans	5 (5)*
Candida parakrusei	3 (3)*
Candida guilliermondi	2 (1)*
Candida krusei	1 (1)*
Candida tropicalis	1 (1)*
Candida (species not identified)	1
No culture	1
Pathologic Findings:	
Mitral valve endocarditis	7
Aortic valve endocarditis	4
Combined mitral and aortic valve endocarditis	2
Right atrial endocarditis	1
Previous valvular damage	11
Embolic phenomenon (kidneys, spleen, brain, and bowels most common sites)	11
Septic emboli	4
Myocarditis	7
Perforation from aortic valve into right atrium	2
Pericarditis	1

*Cultures at autopsy.

SUMMARY

Two cases of Candida endocarditis are reported. Prior treatment of these patients with antibiotics in one case and with antibiotics and steroids in the second case suggests that these therapeutic agents may be important factors in the pathogenesis of the infection. The clinical and pathologic features of previously well-documented cases are also presented.

Treatment with amphotericin B in one case of Candida endocarditis resulted in a prolonged reversal of the positive blood cultures, but the patient ultimately died. This drug appears to be an effective agent in the treatment of systemic fungus infections. We believe that fungus endocarditis will be encountered more frequently because of the increasing incidence of secondary fungus infections.

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An Aid to Identification of the Murmur of Aortic Stenosis With Atypical Localization

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The diagnosis of aortic stenosis is not difficult when the murmur is characteristic and when other signs of the disease are present. However, on occasion, the diagnosis may be overlooked. This is especially true when the murmur is faint at the base and louder at the apex,[1] or when it is exclusively heard there,[2] suggesting that its origin is at the mitral valve. Errors in diagnosis are probably more common in middle-aged or elderly individuals in whom the incidence of aortic valve murmurs is increased,[3] although, at the same time, as a result of a reduction in cardiac output or the presence of changes in chest contour, such murmurs may be faint or nondescript. Coexisting valve lesions may make the diagnosis of aortic stenosis more difficult at any age. Whereas a decade ago the source of difficult systolic murmurs might have been an academic consideration, the recent advances in surgical methodology have given a fresh importance to their accurate localization.

Clinical and phonocardiographic observations in this laboratory have suggested a useful aid in the evaluation of these uncertain systolic murmurs. First, experiences here confirm the earlier observations of Leatham[4] that, when the murmur of aortic stenosis is louder at the mitral area, it retains its diamond-shaped character in phonocardiograms from that region. Furthermore, in the presence of an irregular ventricular rhythm, this murmur exhibits another unique property which may be utilized diagnostically. Since atrial fibrillation is such a constant accompaniment of mitral insufficiency, its presence may encourage the mistaken diagnosis of the latter lesion, and the delineation of a unique property of aortic stenosis in combination with atrial fibrillation should be particularly welcome.

In a previous paper from this laboratory,[5] dealing with the phonocardiographic characteristics of mitral stenosis and insufficiency, it was asserted that typically the murmur of mitral insufficiency remains practically constant in intensity regardless of the preceding diastolic interval (Fig. 6), and that this feature

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This study was done with the aid of a traineeship grant from the Alameda Heart Association.
Received for publication Jan. 25, 1960.
*Mr. Henke is a senior medical student.

could be identified at the bedside as well as by phonocardiograms. In contrast, the ejection murmur of aortic stenosis is very significantly influenced by cycle length, the murmur being loud after long diastoles and faint after short diastoles. The purpose of the present communication is to illustrate this characteristic in more detail.

MATERIALS AND METHODS

The clinical data and phonocardiograms of six patients with the combination of aortic stenosis and atrial fibrillation were studied. In five of these, the diagnosis was confirmed by surgery or physiologic study. Four patients with aortic stenosis and sinus rhythm, and three patients with mitral insufficiency and atrial fibrillation were reviewed for comparison. The patients with mitral insufficiency belonged to the group of 13 patients who, at the time of operation, were found to have strong regurgitant jets. The auscultatory findings and phonocardiograms of these patients are completely reported elsewhere.[5]

All phonocardiograms were recorded with the Sanborn Twin-Beam oscillograph, with the patient in a recumbent position. Carotid and jugular pulses as well as apical impulses were externally recorded with a crystal pickup. Records were made at a paper speed of 75 mm. per second. The light vertical lines represent 0.04-second, and the heavy lines represent 0.20-second, time intervals. Lead II of the electrocardiogram was simultaneously recorded. In labeling the records, the following abbreviations are used: *1*, first heart sound; *2*, second heart sound; *3*, third heart sound; *SM*, systolic murmur; *DM*, diastolic murmur; *G*, gallop; *E*, ejection sound.

In all of the patients with aortic stenosis and atrial fibrillation the peak intensity of the murmur in millimeters of paper deflection was plotted against the preceding diastolic interval in seconds. A segment of a typical strip is shown in Fig. 1. The data were then plotted in scattergram form to show the relationship between murmur intensity and cycle length.

RESULTS

In all six patients with aortic stenosis and atrial fibrillation, the intensity of the murmur was a function of the previous cycle length. Figs. 1-3 are phonocardiograms from the apex or left sternal border on the upper channel and the ECG or carotid pulse on the lower channel. J.S. in Fig. 1 is typical of all the patients studied. Note that as the cycle length increases from 0.83 second to 1.2 seconds, the maximum intensity of the murmur is almost doubled. At the same time, the typical phonocardiographic appearance of an ejection murmur is retained. The scattergrams in Figs. 4 and 5 show how this occurs in strips in which the intensity can be plotted against randomly varying cycle lengths. In Fig. 5,*A*, H.M.C., the linear relationship ceases at a cycle length of 1.0 second. This suggests that at 1.0 second, filling of the ventricle is complete in this particular instance. In contrast, when sinus rhythm was present, the murmur of aortic stenosis was constant in intensity from cycle to cycle in the cases studied here.

When mitral insufficiency and atrial fibrillation were present, the intensity of the murmur was practically independent of cycle length. Figs. 6 and 7 illustrate this point. The phonocardiograms and scattergrams show no variation in the intensity of this murmur with the preceding diastolic interval.

DISCUSSION

The observations presented here received little attention prior to the recent study by Hultgren and Leo.[5] Levine and Harvey[6] published in their monograph

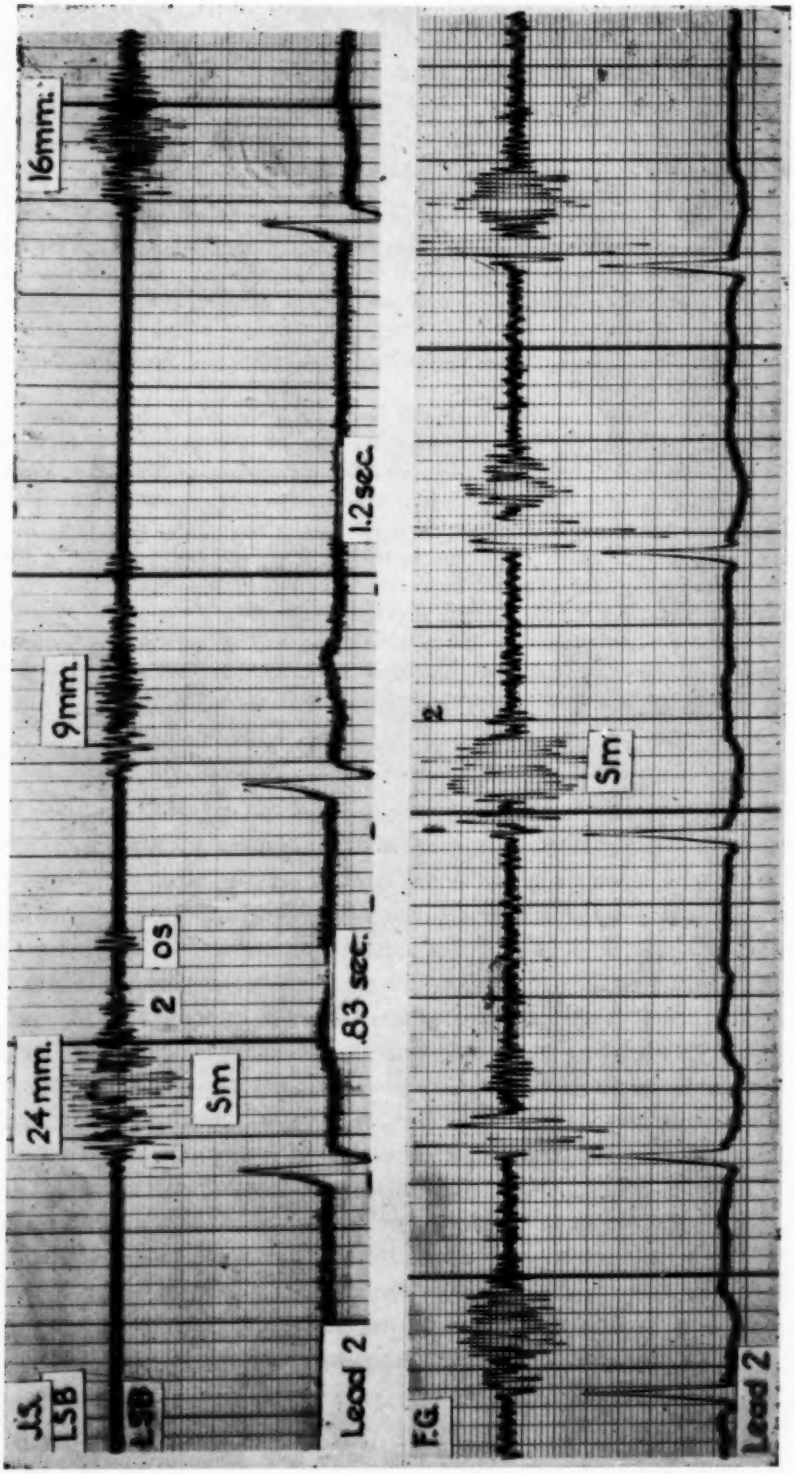

Fig. 1.—Phonocardiograms from the left sternal border in aortic stenosis. The variation of murmur intensity with cycle length is illustrated.

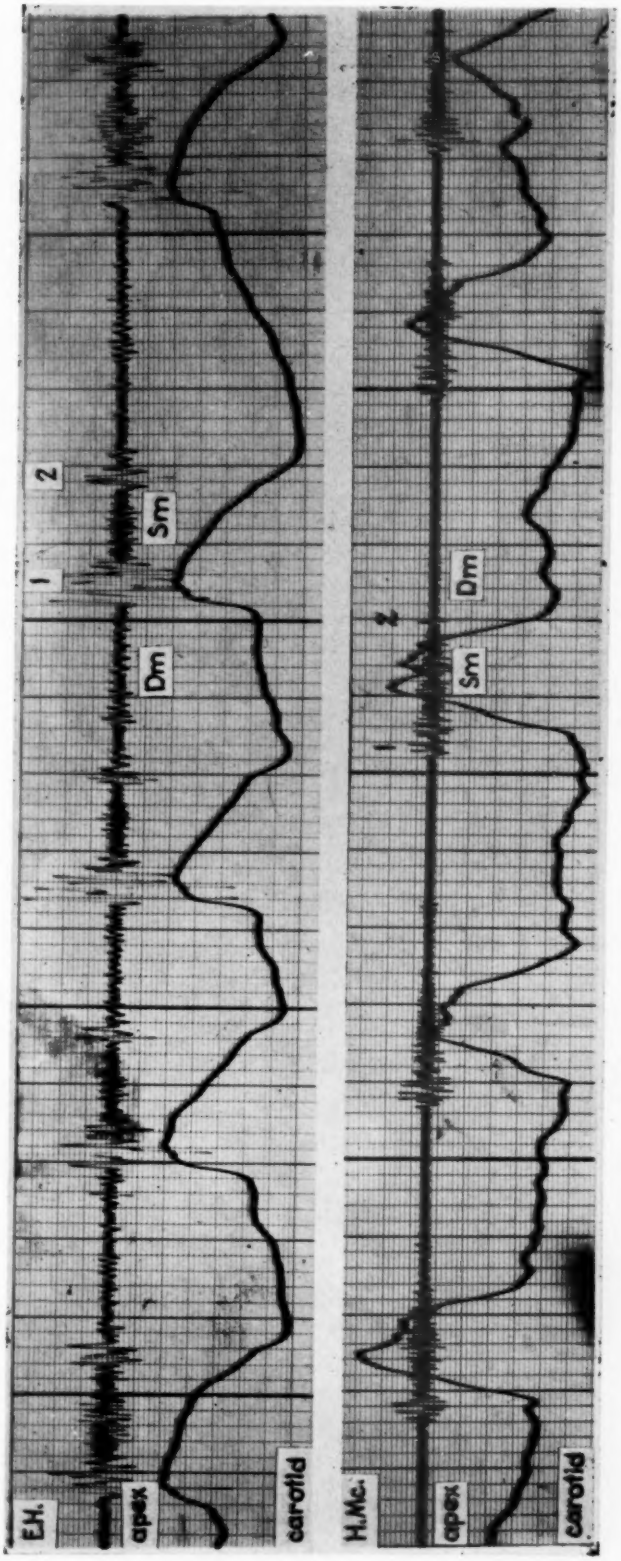

Fig. 2.—Phonocardiograms from apex in aortic stenosis. The murmur intensity varies with cycle length.

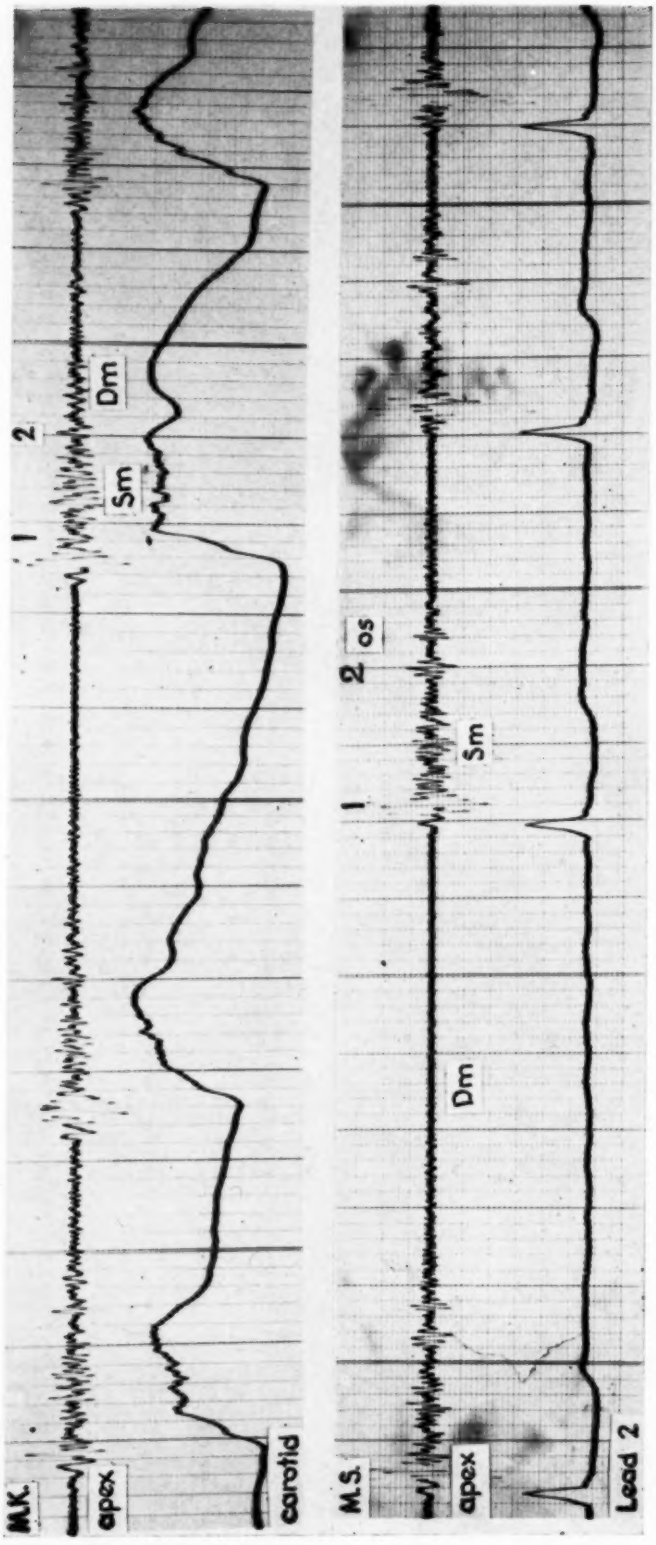

Fig. 3.—Phonocardiograms from apex in aortic stenosis. After short cycles the murmur practically disappears.

a record in which the murmur of aortic stenosis was ". . . fainter with quick beats and louder after long pauses," and Gordon and associates[7] stated that the intensity of the murmur varies directly with the difference in pressure. McKusick[8] showed that with a premature beat the murmur is faint. However, the distinction between the behavior of aortic and mitral murmurs when the cycle length is varied has not been made, nor has the diagnostic application been suggested. Recently, the phenomenon was nicely demonstrated in intra-aortic

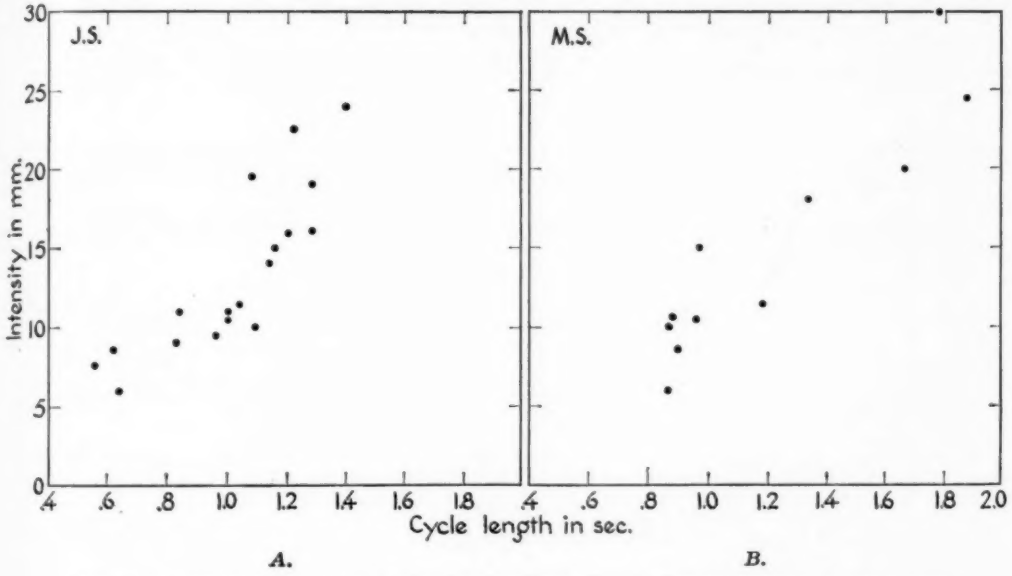

Fig. 4.—*A* and *B*, The murmur intensity of aortic stenosis is plotted against cycle length.

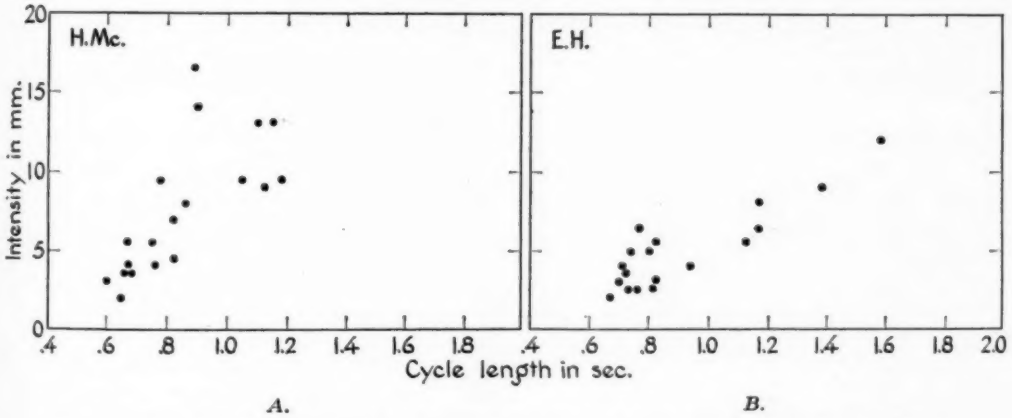

Fig. 5.—*A* and *B*, Aortic stenosis. Murmur intensity and cycle length plotted as in Fig. 4.

phonocardiograms by Liu, but the author does not refer to it in his text.[9] The experience here suggests that these properties are useful diagnostically. Their usefulness is enhanced because they may be appreciated at the bedside with a stethoscope. Although the observations in this study were made in the presence of atrial fibrillation, the same variations occur in any situation in which the stroke volume varies from beat to beat, as illustrated in Fig. 8. Similar observations on

the behavior of pulmonary ejection murmurs have been made in this laboratory. The variations in murmur intensity are, of course, best appreciated when the apical rate is below 100. Increases in heart rate are effected primarily at the expense of the diastolic interval, and the differences in cycle length may become too small to allow variations in murmur intensity. At the other extreme, prolongation of the diastolic interval beyond a critical point may not increase the intensity of the murmur if filling has already been completed. When mitral insufficiency is accompanied by a well-transmitted aortic stenosis murmur, the auscultatory characteristics at the apex may be those of the aortic murmur, and it may be diamond-shaped in phonocardiograms.

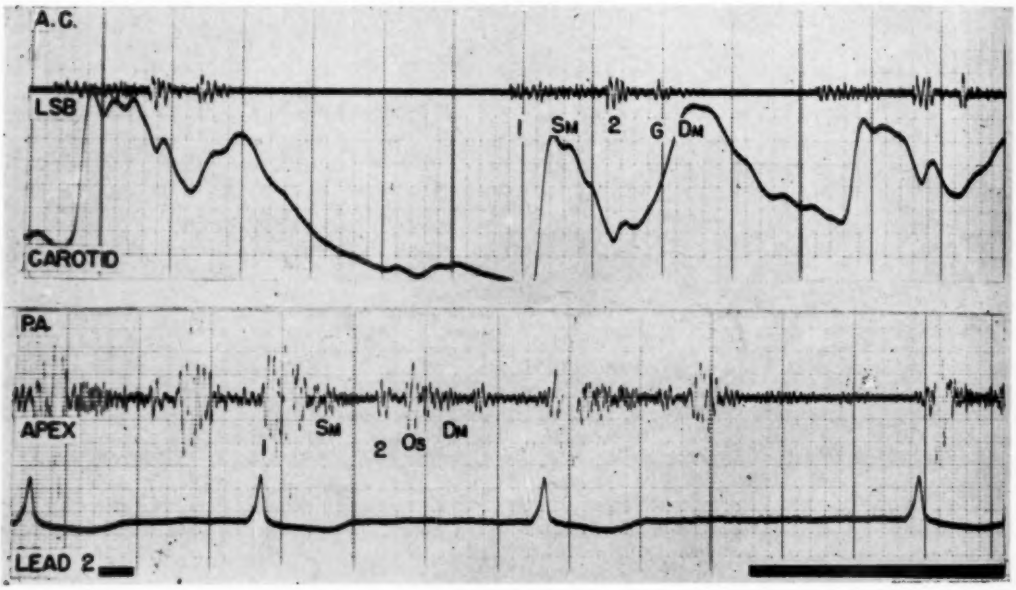

Fig. 6.—Mitral insufficiency. Note lack of variation of murmur intensity although cycle length is very irregular.

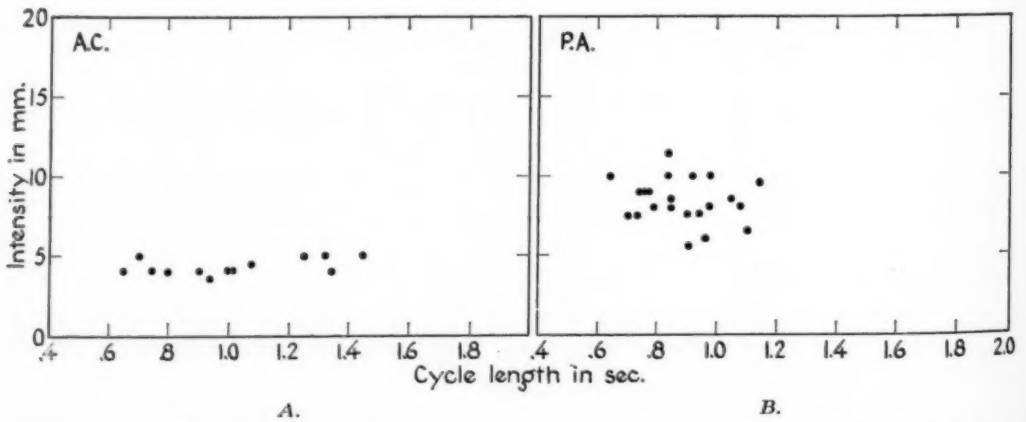

Fig. 7.—*A* and *B*, Mitral insufficiency. The constancy of the murmur intensity is illustrated.

The development of the techniques of left heart puncture and catheterization has made possible a physiologic understanding of the foregoing observations. It is apparent that the time-intensity characteristics of the diamond-shaped murmur of aortic stenosis parallels very closely the time-pressure gradient across a stenotic aortic orifice after the onset of ejection.[8] The peak intensity of the murmur corresponds to the peak of the pressure difference and, probably, ejection velocity across the valve; this appears to just precede the maximum of ventricular pressure almost in mid-systole.[7] The magnitude of the gradient, however, is largely dependent upon the stroke volume, which in cases of atrial fibrillation will vary from beat to beat as the diastolic filling period varies. This is illustrated in Fig. 9, in which left ventricular and brachial arterial pressures are recorded with equisensitive gauges in a patient with aortic stenosis and atrial fibrillation. It will be seen that, after the longer R-R intervals, the maximum gradient is large, whereas after the short R-R intervals, it is much smaller. A plot of this gradient with respect to cycle length was similar to the graphs in Figs. 4 and 5, in which the intensity of the murmur is plotted against cycle length.

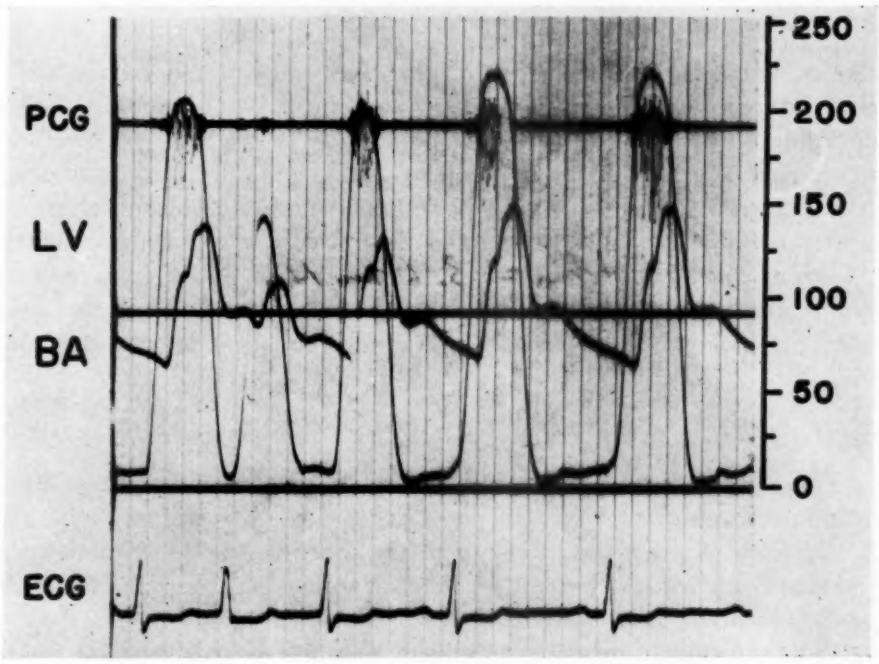

Fig. 8.—Aortic stenosis. Illustration of the variations of the murmur with premature beats and during sinus arrhythmia. The change in intensity parallels the alterations in the gradient across the aortic valve.

The time-pressure gradient relationship in mitral insufficiency contrasts with that of aortic stenosis. The build-up of a ventriculoatrial differential is very rapid, and as the mitral valve is closed, producing the first heart sound, the pressure difference is soon maximal. The left atrial pressure does not rise appreciably during isometric contraction, and its peak is slowly reached late in

systole.[10,11] The gradient, therefore, remains relatively large well into the ejection period and even up to the time of closure of the aortic valve. This latter event occurs early since the backward and forward flows abbreviate the ejection period, and an abnormally rapid run-off of left ventricular pressure has been described.[12] These considerations explain the classic holosystolic murmur of mitral insufficiency, often plateau in form, which persists through the aortic component of the second sound.

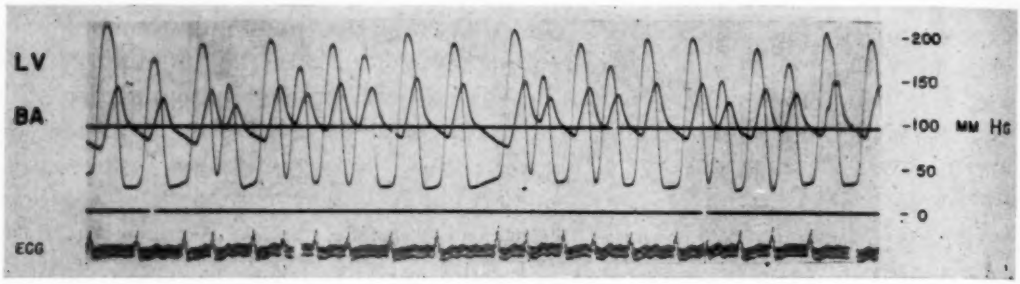

Fig. 9.—Note the variations in the gradient across the aortic valve with cycle length. The gradient is small after short cycles.

The constant intensity of this murmur with varying cycle length is of considerable interest and warrants further combined hemodynamic and phonocardiographic study, especially with reference to the character of the left atrial pressure pulse. Whereas left ventricular systolic pressure will vary sensitively with the preceding diastolic filling period, the pressure-volume characteristics of the atrium must be important determinants of the net ventriculoatrial gradient.[13] When the left atrium is large and distensible and a large end-diastolic gradient is absent, the systolic gradient is of large magnitude even after short diastoles, producing full murmurs of relatively constant amplitude from cycle to cycle.

SUMMARY

1. The phonocardiograms of six patients with aortic stenosis and atrial fibrillation are presented.

2. In each of these the intensity of the murmur varied with the preceding cycle length, being more intense after long diastoles. Scattergrams show that this relationship is practically linear.

3. The murmur of mitral insufficiency exhibits no significant variation with cycle length.

4. It is suggested that these properties may be useful in the diagnosis of murmurs heard maximally or exclusively at the apex.

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Needle Biopsy of the Human Ventricular Myocardium: Review of 54 Consecutive Cases

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Needle biopsy of certain human organs has become an increasingly important procedure. Specimens of tissue so obtained give opportunity for an accurate morphologic study that is offered by no other means. In the diagnosis of lesions of the myocardium, such methods as electrocardiography, various radiologic procedures, heart catheterization, and bacteriologic or viral studies offer only indirect information from which certain presumptive conclusions can be drawn.

Metabolic, inflammatory, fibrotic, and invasive processes of the myocardium can be studied by multiple needle biopsies of the heart.[1-4]

This report presents the findings for the first 54 consecutive patients in whom multiple myocardial biopsies (totaling 150) have been obtained.

MATERIAL AND METHOD

The Terry needle was modified by making it highly flexible with a thin wall. Two cutting teeth were made in the point (Fig. 1). The length was 4 inches; the inside diameters have varied from 0.4 to 1.2 mm. During percutaneous insertion, a blunt trocar was used.*

For all biopsies there was continuous electrocardiographic monitoring with an oscilloscope. After antisepsis and local anesthesia, the skin was nicked and the needle (with the trocar but without a depth guard) was inserted until the heart surface was felt. At this point, pain may normally be experienced and ventricular premature systoles detected (Fig. 2). The trocar was removed and the needle quickly inserted further with a rotary motion and with suction applied by a syringe and then removed. Deliberate oblique punctures not reaching the cavity were usually employed.

Biopsy specimens have been obtained during pericardiotomy, thoracotomy, and cardiac surgery,† and, most commonly, percutaneously. Two sites for percutaneous myocardial biopsy are feasible. The chest may be entered at the left costal-sternal junction (Larry's point) where the needle enters the right ventricle and avoids the lung. This route has been more painful and less certain as a biopsy site because the right auricle is sometimes entered. The second route (probably preferable) is in the apex or outflow tract of the left ventricle, at the site employed for left ventricular catheterization by Brock[5] (Fig. 3). Usually two, three, or four biopsy speci-

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This work was supported by the Eustice Fund.

Received for publication Jan. 15, 1960.

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†We are indebted to Dr. George Holmes and Dr. Egbert Fell for biopsy specimens taken during surgery.

mens were taken; the number was determined by the adequacy of the specimen obtained and the response of the patient. All biopsies were performed as major procedures, with preparation for emergency use of a defibrillator, pacemaker, oxygen, and the possible necessity of open thoracotomy. After the biopsy the patient was kept supine and quiet for 3 hours. Repeated observations of the pulse rate and rhythmicity, heart size, and venous pulse were recorded.

A fragment of myocardium about 1 by 3 mm. was obtained. The specimen was expressed into a 10 per cent buffered formalin solution for fixation. The entire block was cut serially or subserially. Sections were stained with hematoxylin and eosin, Mallory, Gömöri's trichrome, and also impregnated with silver according to the method described by Gömöri.

No patients with any of the following conditions were biopsied: (1) acute cardiac infarction, (2) severe congestive failure (Grade 4), (3) hypoprothrombinemia or other hemorrhagic diatheses, (4) purulent pericarditis, (5) acute infections of the lung if the lung was to be traversed in an apical biopsy, (6) active ventricular arrhythmias.

Indications.—By preference, biopsies were performed on patients with serious cardiomegaly or myocardial disease of undeterminable etiology. Patients with varied pathologic conditions in which cardiac involvement was probable were also biopsied.

RESULTS

One hundred and fifty biopsy specimens were removed from 54 patients, without mortality or serious morbidity demanding therapy. The most common but not invariable reaction was ventricular arrhythmia, which consisted of scattered ventricular ectopic beats or short runs of ventricular tachycardia, the most prolonged of which is presented in Fig. 2. There was no serious bleeding in this series. During thoracotomy, deliberate through-and-through puncture of the right ventricular wall seemed to ooze slightly longer than did such a puncture of the left venticle.

One autopsy performed in a patient who died of a cerebral hemorrhage 5 days after the biopsy showed approximately a one-fourth inch circle of subepicardial hemorrhage at the site of puncture. An autopsy on a second patient several months after biopsy showed a minute scar in the epicardium, with a hair-like adhesion to the parietal pericardium.

Interpretations of the microscopic sections were all made initially by one person without prior knowledge of the clinical diagnosis. The results are presented in Table I. The relatively small number of biopsies obtained in any one

TABLE I. MICROSCOPIC INTERPRETATIONS OF THE 54 VENTRICULAR NEEDLE BIOPSIES

INTERPRETATION	NUMBER OF CASES
Normal myocardium	13
Myocardial fibrosis	12
Hypertrophied myocardial fibers with bulky nuclei	4
Acute rheumatic myocarditis	1
Myocardial fibrosis following rheumatic myocarditis	1
Tuberculous pericarditis with inflammatory reaction in muscle	5
Lipomatosis	1
Collagen deposits	1
Inflammatory reaction in Boeck's sarcoid	1
Fibroelastosis	1
Acute myocarditis, nonspecific	1
Unsatisfactory specimen	13

category in this series reflects the diverse character of the patients studied. There were 13 failures, largely in the early part of the series, to obtain a satisfactory specimen of myocardium. Artefacts and distortion produced by fragmentation of the specimen constituted a problem which has decreased in importance as skill in expelling the biopsy specimen from the needle and in handling it during staining has been acquired.

The following cases are illustrative of the information obtained by biopsy. These cases were chosen not only to illustrate the value of myocardial biopsy in each, but also to emphasize certain clinical problems.

CASE REPORTS

CASE 1.—The patient was a 15-year-old Negro boy who had had no serious illnesses prior to the onset of the present illness. Approximately 2 weeks before admission to Cook County Hospital, he began to experience easy fatigability, irritability, and orthopnea which progressed to cough and hemoptysis.

Physical examination revealed a normally built but seriously ill young man who had a low-grade fever (99-101° F.) and tachycardia and tachypnea. The blood pressure in the left arm was 148/110 mm. Hg, and the pulse was absent in the right carotid, subclavian, and radial arteries.

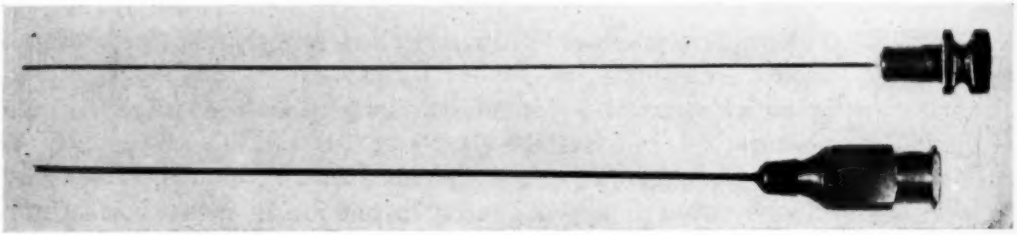

Fig. 1.—Biopsy needle used, with 1.1 mm. inside diameter. Note notched cutting edge.

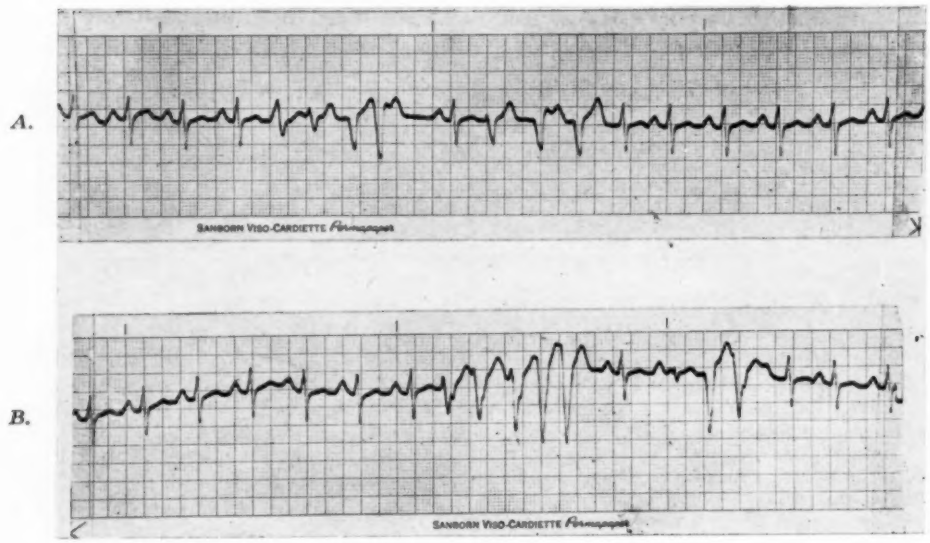

Fig. 2.—*A* and *B*, Electrocardiograms taken during two separate biopsies (Lead II).

Venous pressure was normal, but fine râles were heard in both lung bases. The heart was grossly enlarged, with a diffuse precordial heave visible in the left anterior axillary line. There were no thrills, but a Grade 4 holosystolic murmur was heard over the entire precordium, and a to-and-fro pericardial friction rub was heard at the apex. The heart tones were normal. There was a leukocytosis of 11,100, with 72 per cent polymorphonuclear cells; erythrocytes revealed toxicity, and target cells and their sedimentation rate was 32 mm./hr. The blood Kahn test was negative, and there was persistent albuminuria. X-ray films of the heart revealed cardiac enlargement, with bulging of the left pulmonary conus region. Increased hilar vascular markings were seen in both lungs. The ECG showed sinus tachycardia, left axis deviation, and horizontal electrical position. The T wave was inverted in Leads I, II, III, aV_R, aV_L, aV_F, V_{1-6}, without elevation of J, and was compatible with the pericarditis. Blood cultures were negative, and the patient remained febrile and gravely ill in spite of penicillin and aspirin therapy. Skin tests with old tuberculin were negative. Pericardiocentesis produced a small quantity of clear, straw-colored fluid which was sterile on culture. Left ventricular biopsy was done percutaneously at the time of pericardiocentesis. Precordial pain became marked, and the patient expired suddenly on the eleventh day of hospitalization.

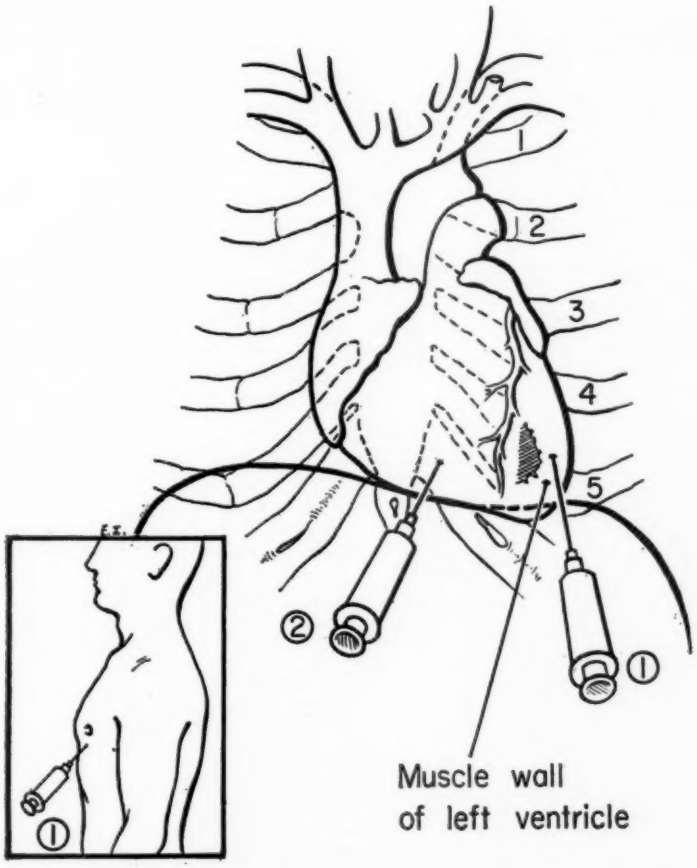

Fig. 3.—*1*, The needle is inserted into the fifth or fourth left intercostal space, 10 to 15 mm. to the left of the palpable apex beat. *2*, The needle is inserted at Larry's point and upward through the diaphragm.

The clinical diagnosis was uncertain; rheumatic heart disease with mitral insufficiency, cardiac failure, and bronchopneumonia were thought to be definite. Proof of bacterial endocarditis, Marfan's syndrome, or of the cause of the pericarditis was lacking. Autopsy permission was refused.

Multiple biopsies of the left ventricular outflow tract revealed normal ventricular myocardium (Fig. 4). This case presented unequivocal evidence of fatal cardiac disease in which no *microscopic* alteration of the myocardium could be demonstrated by four random needle biopsies. Further steps, such as microchemical studies, might have been of aid.

CASE 2.—The patient was a 44-year-old white man who had a right upper and middle lobectomy on Feb. 14, 1959, for removal of a firm nodular mass which measured 3 by 4 cm., and which on microscopic section was found to be "a pulmonary granuloma, most consistent with tuberculosis." He was admitted to Cook County Hospital (on Sept. 18, 1959) 7 months later with a 6-week history of weakness, exertional dyspnea, and swelling of both lower extremities. Routine blood and urinalysis were normal. The chest x-ray film showed a rectangular density in the right upper lung, with the trachea deviated to the right, and the upper right rib intercostal spaces narrowed and the right diaphragm elevated. There was no radiologic evidence of congestive failure, and the heart size was normal.

Right heart catheterization revealed a main pulmonary arterial pressure of 35/20 mm. Hg and right ventricular pressure of 35/0 mm. Hg. The ECG was normal. Angiocardiography revealed only distortion of right pulmonary arterial distribution. Two myocardial biopsies were done with a 1.1-mm. needle at the apex of the left ventricle. The patient responded to digitoxin and conventional cardiac therapy and was discharged in a compensated state; the diagnosis was heart failure of uncertain cause, demonstrated to be associated with myocardial fibrosis and hypertrophy.

The microscopic section (Fig. 5) revealed extensive replacement of the myocardium by fibrous connective tissue; in some areas the tissue was very hypocellular. The adjacent myocardial fibers contained bulky nuclei. This was interpreted as myocardial fibrosis and hypertrophy of myocardial fibers. This case is illustrative of the microscopic alterations most frequently encountered in this series. Myocardial fibrosis was encountered in diverse clinical conditions and age groups.

CASE 3.—The patient was a 41-year-old Negro cook who denied any history of rheumatic diathesis. An enlarged heart of uncertain cause (attributed to rheumatic fever by his physician) was detected 11 months prior to admission, when he first became short of breath. Two weeks prior to admission to Cook County Hospital, he developed extreme exertional dyspnea, orthopnea, and substernal pain which did not radiate, but was relieved by sitting up.

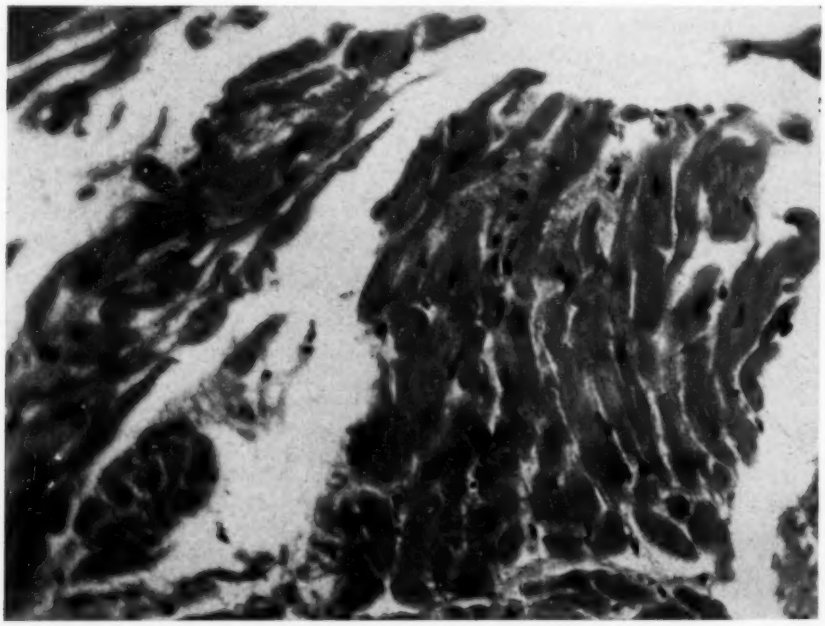

Fig. 4.—Normal myocardium (Case 1).

At the time of his admission the blood pressure was 100/85 mm. Hg, the venous pressure was normal, the pulse rate was 100 and regular, the respirations were 48 per minute and Cheyne-Stokes, and the temperature was 99.0° F. Fine râles were heard in both lung fields. There was marked cardiomegaly to the left, with the apex diffuse and heaving in the sixth intercostal space at the mid-axillary line. Heart tones were muffled and no murmurs were heard. The liver was

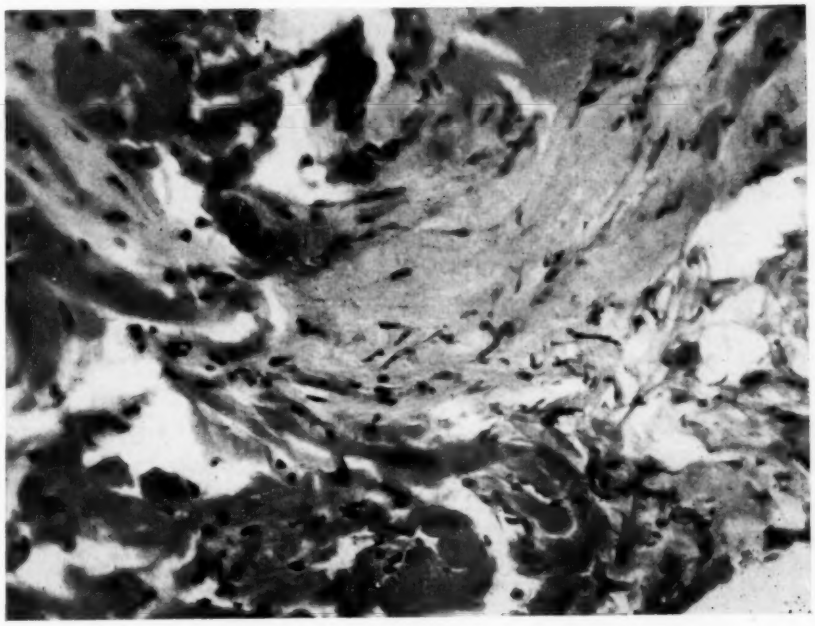

Fig. 5.—Myocardial fibrosis and hypertrophy of myocardial fibers (Case 2).

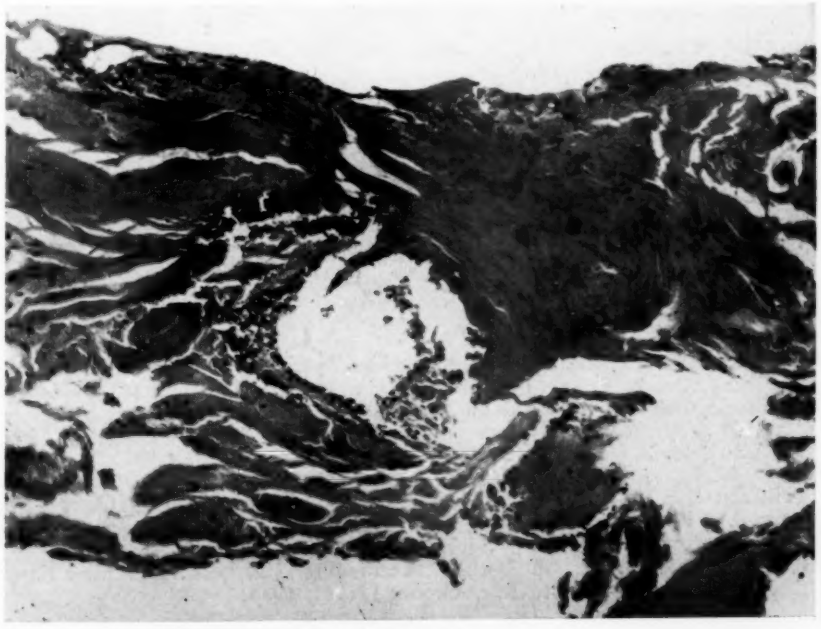

Fig. 6.—Focal myocarditis (Case 3).

enlarged and there was moderate pretibial edema. Routine blood counts were normal except for leukocytosis. X-ray examination of the chest revealed an enlarged heart, especially to the left, with hazy densities in both lung fields. The electrocardiogram showed T_1 isoelectric, T_2 and T_3 negative, sinus tachycardia, T in Leads V_{1-4} normal, and T in Leads V_{5-6} inverted. The temperature rose to 103-104° F. in spite of antibiotics, and myocardial biopsy was done because "toxic myocarditis" due to overwhelming pulmonary infection and severely damaged heart was suspected. The patient died on the sixth hospital day.

The diagnosis of "myocarditis" was substantiated by the biopsy. The microscopic section (Fig. 6) of the myocardial biopsy specimen revealed connective tissue stroma and vascular structures, striated muscle, and areas with small foci of chronic inflammatory cells, chiefly histiocytes intermingled with a few polymorphonuclear leukocytes.

DISCUSSION

The importance of specific etiological and pathologic diagnosis in the management of diseases of the myocardium is obvious as a foundation for therapy. This series shows that biopsy of the human ventricular myocardium is feasible and is adequate to establish certain microscopic diagnoses. In addition to the morphologic studies, it may be possible to adapt certain biochemical procedures to help in studies of myocardial metabolism.

Diffuse lesions, such as fibrosis, acute myocarditis, fibroelastosis, collagen disorders, and lipomatosis, can be identified and were diagnosed in this series. Certain lesions of the myocardium are focal and may be undetected by biopsy. Correlation between myocardial histopathology, function, and clinical diagnosis can be made in certain cases.

CONCLUSIONS

The results obtained in a series of 54 consecutive patients subjected to multiple needle biopsy of the ventricular myocardium are presented.

Specimens of tissue were satisfactory for the microscopic detection of normal myocardium, myofibrosis, diffuse myocarditis, fibroelastosis, collagen disorders, and lipomatosis. These specimens were obtained without mortality or serious morbidity.

The authors gratefully acknowledge the technical contribution of Mr. Fred Bujakowski, Medical Technician, Department of Pathology, Cook County Hospital. Dr. Paul B. Szanto, Chief of Pathology, Cook County Hospital, reviewed the pathologic sections.

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Specificity of the Current Electrocardiographic Criteria in the Diagnosis of Left Ventricular Hypertrophy

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The usefulness of the electrocardiogram in the diagnosis of left ventricular hypertrophy (LVH) is well recognized. Different sets of criteria, based largely on clinical grounds, have been proposed by various authors. The accuracy of these criteria is best determined by pathologic correlation. In a previous study from this laboratory, Scott and associates[1] analyzed the electrocardiographic findings in 100 cases of pure LVH as proved at autopsy. It was found that by using a combination of the various electrocardiographic criteria, 96 per cent of the cases could be correctly diagnosed. As emphasized, this study tested only the sensitivity of the various criteria and not their degree of specificity, i.e., the occurrence of false positive diagnoses. The present electrocardiographic and pathologic analysis was conducted in an attempt to evaluate the latter aspect.

MATERIALS AND METHODS

The electrocardiograms of all autopsied patients from the Cincinnati General Hospital in a 5-year period were reviewed. All cases which met one or more electrocardiographic criteria for LVH (described below) were selected. The first 100 consecutive patients who had a 12-lead electrocardiogram recorded within 3 months of death (and who showed no evidence of myocardial infarction on later review of the pathologic findings) were used as the material for this study (Group 1). All cases of bundle branch block were excluded. The age of the patients ranged from 16 to 92 years.

A control series of another 100 consecutive adults autopsied at Cincinnati General Hospital (Group 2), who had electrocardiograms recorded within 3 months of death, was used to determine the incidence of anatomic LVH in the group when the electrocardiographic findings were not taken into consideration.

The following electrocardiographic criteria for the diagnosis of LVH were employed: (1) Left axis deviation with R_1 plus S_3 exceeding 25 mm.; S-T depression greater than 0.5 mm. in Lead I or a T wave less than 1 mm. in Lead I (in the absence of digitalis). (2) A negative deflection in Lead aV_R greater than 14 mm. (3) An R wave in Lead aV_L greater than 11 mm. in a horizontal heart. (4) An R wave in Lead aV_F greater than 20 mm. in a vertical heart. (5) An R wave in Lead V_5 or Lead V_6 greater than 26 mm. (6) R in Lead V_5 or Lead V_6 plus S in Lead V_1 exceeding 35 mm.

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Received for publication Jan. 18, 1960.

(7) QRS duration increased to 0.10 or 0.11 second. T-wave inversion in Lead V_5 or Lead V_6 with S-T depression (in the absence of digitalis). (8) Delay in the onset of the intrinsicoid deflection between 0.05 and 0.07 second in Lead V_5 or Lead V_6.

The foregoing criteria were derived by combining the various sets of criteria reviewed by Scott and associates,[1] which were found by them to give a high positive result.

The pathologic criteria for ventricular hypertrophy were based on both the weight of the heart and the thickness of the ventricular wall. The weight of the heart was considered to be increased if it exceeded the upper limit of normal for the patient's body length, as determined by Zeek.[2] Left ventricular hypertrophy was considered to be present if the total weight of the heart was increased and the left ventricular thickness was 13 mm. or more. Right ventricular hypertrophy (RVH) was considered to be present if the total weight of the heart was increased and the right ventricle was 5 mm. or greater in thickness, if not dilated, or 4 mm. if dilated as stated definitely in the autopsy protocol. The ventricular measurements were made by different prosectors over a period of years, but the technique was uniform. The measurements represent the greatest thickness from epicardium to endocardium, and care was taken not to include the thickness of the papillary muscles.

RESULTS

Among the 100 cases which met the electrocardiographic criteria of LVH (Group 1), there were (Table I), anatomically, 44 cases of isolated LVH, 45 cases of combined ventricular hypertrophy (CVH), 1 case of isolated RVH, 1 case with no ventricular hypertrophy, and 9 cases of questionable hypertrophy. In 3 of the questionable cases the weight of the heart was increased but the measurements of the ventricular wall were normal. In the other 6 the weight of the heart was normal but the thickness of one or both ventricles was increased. Thus, more than 89 per cent of the cases showed LVH either in isolated or combined form. They will be called the anatomic positive group.

The incidence of LVH in the control series (Group 2) is shown in Table II. Among the 100 patients there were 35 with isolated LVH, 30 with CVH, 3 with isolated RVH, and 32 with no, or questionable, ventricular hypertrophy. Thus, the total number of patients showing either isolated LVH or CVH (65) in this group is definitely less than that of Group 1. Statistically, the difference is highly significant ($p < 0.001$).

Table III indicates how often each of the various criteria was used in making the electrocardiographic diagnosis of LVH in Group 1. For the purpose of simplicity, the criteria were grouped in relation to voltage, onset of intrinsicoid deflection, QRS interval, and S-T-T changes. High voltage was the most frequently positive criterion, being present in all except 2 cases. In the 89 cases of anatomic LVH, high voltage was encountered in the precordial leads in 79 and and in the limb leads in 46. Delay in the onset of the intrinsicoid deflection in Leads $V_{5,6}$ occurred in 33 cases. Prolongation of the QRS interval was found in 21 cases. S-T-T abnormalities occurred in 40 of the 45 cases in which no digitalis was administered. Among the 11 questionable and false positive cases, there was increased voltage in all of them in the precordial leads but in none in the limb leads. Delay in the onset of the intrinsicoid deflection in Leads $V_{5,6}$ and prolongation of the QRS interval each occurred in only one case. S-T-T abnormalities were present in 5 of the 9 cases in which no digitalis was given.

TABLE I. AN ANALYSIS OF THE AUTOPSY FINDINGS WITH REGARD TO VENTRICULAR HYPERTROPHY IN 100 CASES OF LVH DIAGNOSED BY ELECTROCARDIOGRAM (GROUP 1)

AUTOPSY FINDINGS	NUMBER OF CASES AND PERCENTAGE OF TOTAL
Isolated LVH	44
CVH	45
Isolated RVH	1
No ventricular hypertrophy	1
Questionable cases	
Increased weight but normal ventricular measurements	3
Normal weight but increased ventricular measurements	6
Total	100

TABLE II. THE INCIDENCE OF VENTRICULAR HYPERTROPHY IN 100 CONSECUTIVE AUTOPSY CASES IRRESPECTIVE OF THE ELECTROCARDIOGRAPHIC FINDINGS (GROUP 2)

AUTOPSY FINDINGS	NUMBER OF CASES AND PERCENTAGE OF TOTAL
Isolated LVH	35
CVH	30
Isolated RVH	3
No ventricular hypertrophy	9
Questionable cases	
Increased weight but normal ventricular measurements	15
Normal weight but increased ventricular measurements	8
Total	100

TABLE III. COMPARISON OF THE CRITERIA USED FOR THE DIAGNOSIS OF LVH IN THE ANATOMIC POSITIVE AND QUESTIONABLE AND FALSE POSITIVE GROUPS

ELECTROCARDIOGRAPHIC CRITERIA FOR LVH	ANATOMIC POSITIVE GROUP (LVH, CVH) (89 CASES)	ANATOMIC QUESTIONABLE AND FALSE POSITIVE GROUP (11 CASES)	TOTAL (100 CASES)
High voltage, total	87	11	98
Standard and unipolar limb leads			
As the only sign of LVH	2	0	2
Used in combination with other signs	44	0	44
Precordial leads			
As the only sign of LVH	11	5	16
Used in combination with other signs	68	6	74
Delay in OID			
As the only sign of LVH	0	0	0
Used in combination with other signs	33	1	34
QRS-interval prolongation*	21	1	22
S-T-T abnormalities*			
(in the absence of digitalis)	40 (45)†	5 (9)†	45 (54)†

*Used only in combination with other signs.
†Total number of cases in each group that did not receive digitalis.
OID: Onset of intrinsicoid deflection.

An attempt was made to elicit evidence which would differentiate the group of CVH from that of isolated LVH, thus increasing the specificity of the criteria. Table IV is an analysis of the cases in which the electrocardiograms also met one or more of the usual criteria for RVH.[3,4] There were 22 cases, with 10 showing CVH and 12 showing isolated LVH at autopsy. Three of the 4 cases with R in Lead V_1 of 7 mm. or greater, and 9 of the 18 cases with R in Lead V_1 plus S in Leads $V_{5,6}$ of 10.5 mm. or greater had only isolated LVH. The only criteria which indicated the presence of coexisting RVH without a false positive diagnosis were: R wave greater than S wave in Lead V_1, and R wave in Lead aV_R 5 mm. or greater. Table V correlates the electrical positions of the heart with the anatomic findings. There were no essential differences in the distribution of the electrical positions between the group with anatomic isolated LVH and that with CVH.

TABLE IV. ANATOMIC FINDINGS IN CASES WHICH MET ONE OR MORE CRITERIA FOR RVH IN ADDITION TO THOSE FOR LVH

CRITERIA FOR RVH*	NUMBER OF CASES	ANATOMIC FINDINGS	
		LVH	CVH
R in Lead V_1 7 mm. or more	4	3	1
S in Lead V_1 less than 2 mm.	0	0	0
R greater than S in Lead V_1	1	0	1
R in Lead V_1 plus S in Lead V_5 (V_6) 10.5 mm. or more	18	9	9
QID in Lead V_1 0.035 to 0.05 sec.	0	0	0
qR pattern in Lead V_1 or Lead V_{3R}	0	0	0
S-T segment depressed and T inverted in Lead V_1	0	0	0
R in Lead aV_R 5 mm. or more	1	0	1
Cases which met two or more of above criteria	1	0	1
Total number of cases which met one or more criteria	22	12	10

*The criteria for RVH are a modification of those suggested by Sokolow and Lyon[3] and Myer and associates.[4]

DISCUSSION

Our results indicate that the current electrocardiographic criteria for the diagnosis of LVH are quite satisfactory, because 89 per cent of the cases were confirmed by autopsy examination. The findings are highly significant statistically when compared with those obtained from the control series ($p < 0.001$). However, about half actually had CVH instead of isolated LVH. The relatively high incidence of anatomic LVH (65 per cent) among the control series, moreover, would suggest that the current electrocardiographic criteria for LVH may not be as specific as our results would indicate, since this fact undoubtedly will reduce the chance of making a false positive electrocardiographic diagnosis. Although such a pitfall can scarcely be avoided because of the prevalence of heart disease among the general autopsied adult subjects, it nevertheless should be recognized during the evaluation of the findings.

Recently, Selzer and associates,[5] in a similar study of 108 cases with electrocardiographic evidence of LVH, found 75 cases with anatomic LVH, 16 with borderline LVH, and 17 with no LVH. These authors considered any abnormally heavy heart to have LVH, and a left-to-right ventricular wall thickness ratio of 3:1 or less to indicate additional RVH. With this method, hearts with anatomically isolated RVH might be listed erroneously as having associated LVH, although it is true that this seldom happens in the presence of an electrocardiographic pattern of LVH. The method of selection used by these authors, however, would reduce the number of cases of CVH, since those hearts in which the right ventricular thickness was increased, but not in proportion to the increase of the left ventricle, would be classified as instances of isolated LVH instead of CVH. This probably explains why only 11 of their cases were considered as CVH.

TABLE V. COMPARISON OF THE ELECTRICAL POSITION OF THE HEART IN ANATOMIC ISOLATED LVH AND CVH

ELECTRICAL POSITIONS	ANATOMIC FINDINGS	
	LVH	CVH
Horizontal	11	14
Semihorizontal	5	4
Intermediate	18	19
Semivertical	4	4
Vertical	6	4
Total	44	45

High voltage in the precordial leads was the most sensitive criterion in our study since nearly 90 per cent of the anatomic positive cases could be diagnosed by this criterion alone. However, it was the least specific, because among the 16 patients who had high QRS voltage in the precordial leads as the only sign of LVH, 5 did not have LVH anatomically. This finding agrees with a recent clinical study in which Cumming and Proudfit[6] found that in an unselected group of otherwise normal electrocardiograms in which the sum of S in Lead V_1 and R in Lead V_5 exceeded 35 mm., 39 per cent came from patients with no clinical evidence of cardiac disease. This was not an unexpected finding, since, as with most screening tests, the method which is most sensitive is usually least specific. The normal variations of precordial voltage with different body builds makes it very difficult to define normal limits. Increased voltage in the limb leads, however, is more specific, since in the present study all such cases had LVH at autopsy.

The fact that a much larger percentage of the anatomic positive cases also had delay in the onset of the intrinsicoid deflection in Leads $V_{5,6}$, prolongation of QRS intervals, and S-T-T abnormalities indicate the value of these findings as supporting criteria. It is interesting to note that although the presence of a delay in the onset of the intrinsicoid deflection alone was considered as sufficient to indicate LVH, in none of the cases did it have to be relied upon as the only sign.

In the presence of LVH, the electrocardiographic diagnosis of coexisting RVH generally has been considered to be difficult. Levine and Phillips[7] diagnosed correctly only 2 of 26 cases of CVH. In a larger series, Lipsett and Zinn[8] were able to identify 10 of 73 cases of anatomically proved CVH. The criteria for RVH which they found useful in those 10 cases were: S wave in Leads $V_{5,6}$ greater than 7 mm.; R wave in Lead V_1 plus S wave in Lead V_5 greater than 10.5 mm.; R wave in Leads $V_{5,6}$ less than 5 mm.; large P waves in Leads II and III. In another electrocardiographic and pathologic study, Pagnoni and Goodwin[9] recognized 13 of 51 cases of CVH. They found that the direct evidence of RVH, such as R to S ratio in Lead V_1 greater than 1 and delay in onset of intrinsicoid deflection in Lead V_1 was consistently masked in the presence of LVH. However, they believed that a combination of features of LVH, with the S wave greater than the R wave in Lead V_5 and the R wave greater than the Q wave in Lead aV_R or an inverted T wave in Lead V_1, was diagnostic of CVH, and that the association of a vertical heart with signs of LVH was highly suggestive, although not diagnostic, of CVH.

Our results failed to verify the usefulness of these signs and further emphasized the difficulty in differentiating CVH from isolated LVH electrocardiographically. Although 10 out of 45 cases of anatomic CVH could be diagnosed as such electrocardiographically, 12 of 44 cases of isolated LVH were also erroneously diagnosed electrocardiographically as CVH. This lack of specificity was especially true in those cases in which the diagnosis of coexisting RVH was based upon tall R waves in Lead V_1 or deep S waves in Leads $V_{5,6}$. The presence of LVH appeared to render these criteria unreliable. The only criteria which did not give any false positive results in this series were an R wave greater than the S wave in Lead V_1 and an R wave in Lead aV_R greater than 5 mm. However, the number of cases (2) is too small to draw any conclusion as to the significance of these findings. Similarly, our data show that the association of a vertical heart with signs of LVH is also a nonspecific finding and does not necessarily indicate the coexistence of RVH anatomically.

SUMMARY AND CONCLUSION

An analysis of the autopsy findings in 100 cases of left ventricular hypertrophy (LVH), diagnosed by the electrocardiogram, revealed 44 cases of isolated LVH, 45 cases of combined left and right ventricular hypertrophy (CVH), 1 case of isolated right ventricular hypertrophy (RVH), 1 case of no ventricular hypertrophy, and 9 cases of questionable hypertrophy.

High voltage in the precordial leads was the most useful but least specific criterion for LVH. The presence of increased voltage in the limb leads or other signs in addition to the high voltage increased the specificity.

Differentiation of CVH from isolated LVH by the electrocardiogram was rarely possible by the currently available methods. The presence of anatomic LVH made some of the electrocardiographic criteria for RVH unreliable.

The authors wish to thank Dr. Noble O. Fowler for his helpful comments and suggestions.

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Congenital Atresia of Mitral and Aortic Valves With Vestigial Left Ventricle (Three Cases)

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INTRODUCTION

The improvement in surgical techniques available for correction of congenital cardiac anomalies has led to the necessity for more exact description and classifications. It is as important to be able to analyze cases unsuitable for surgery as to identify those which will benefit. One of the more recent concepts to be formulated as a result of closer study of congenital cardiac defects is the so-called "hypoplastic left heart syndrome."[1,2] Included under this title are cases showing an extremely small left ventricle together with aortic and mitral atresia. In addition, all degrees of mitral and aortic stenosis with left-sided hypoplasia are described, and the most mild examples of the syndrome show only hypoplasia of the aortic arch. This discussion is concerned with the most severe examples, in which the left ventricle is vestigial and the mitral and aortic valves are atretic.

In reviewing the literature on this subject, it becomes apparent that there has been considerable difference in the usage of terms among various authors. Thus, some have tried to assess mitral and aortic valve atresia in terms of function, and in this way have included examples of extreme stenosis in the same group with the cases of atresia.[3,4] In the past, many observers have either overlooked the hypoplastic left ventricle or failed to state whether or not they have searched for it.[5-11] The difficulty in finding the hypoplastic ventricle, and the tendency, therefore, to label these cases as "cor triloculare biatriatum" is well recognized.[12,13,14] For these reasons it is not considered profitable to undertake a detailed assessment of the exact number of cases of this syndrome which may have appeared in the literature. This is particularly true of cases described in the last century.[15,16,17]

It is the purpose of this paper to present three cases of the most extreme variety of this syndrome. They showed mitral and aortic valve atresia with

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Received for publication Jan. 25, 1960.
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extreme hypoplasia of the left ventricle, intact interventricular septum, a defect of the interatrial septum, patent ductus arteriosus, and hypoplasia of the ascending aorta. Few examples of this combination of abnormalities have been described. It appears to fall into that group which, according to Abbott,[18,19] constitutes "a special type of cor triloculare biatriatum." Mönckeberg[14] has called it "cor pseudo-triloculare." In our review of the literature, we have been able to find only three cases with sufficient details to make it possible to identify them as similar to the hearts reported upon here.[13,20,21] We have excluded cases in which no adequate description was given of the presence or absence of a left ventricle,[5-11] cases in which interventricular septal communication existed,[12,22-29] and cases in which aortic or mitral valves were stenotic rather than atretic.[26,30-42]

REPORT OF CASES

In view of the similarity of histories and autopsy findings in these cases, they will be presented together. The three mothers (Negroes, aged 25, 33, and 21 years) each had six previous children, all of whom had survived except one. None gave any history of any abnormalities during the current pregnancies except one who had a mild upper respiratory infection with pyrexia at the third month. Each delivery was without incident at term. The weights of the three babies (see Table I) were: 3,615 grams (Case 1), 2,380 grams (Case 2), and 3,100 grams (Case 3). No cyanosis was observed at birth. At 20 hours (Case 1), 24 hours (Case 2), and 72 hours (Case 3), respiratory difficulty and cyanosis developed and in each case progressed, despite treatment with oxygen, digoxin and Levophed. Death occurred at 30 (Case 1), 36 (Case 2), and 80 hours (Case 3). Radiographs of the chest were performed in each case and showed the heart size to be normal and the lung fields clear. Electrocardiograms demonstrated depression of the S-T segment, with right ventricular hypertrophy in Case 1. In Case 2, evidence was found which was thought by the cardiologist to be suggestive of a single ventricle.

At autopsy, all three children were observed to have been well nourished. A careful search revealed no abnormalities outside the cardiovascular system. Congestion of the lungs and liver was seen in all three cases. In Case 2, congestion was also seen in the gastrointestinal tract. No congenital abnormalities were found outside the heart. The pulmonary blood vessels showed nothing remarkable.

DESCRIPTION OF HEARTS

The weights of all three hearts were within normal limits. Each functioned as a three-chambered organ with vestigial left ventricle (Fig. 9, *Left*). The venous return from the systemic and pulmonary circulations was normal. No extracardiac arteriovenous shunts were discovered. The superior and inferior venae cavae entered a dilated right atrium. The pulmonary veins entered a small left atrium. The coronary venous return was normal and the coronary sinus entered the right atrium in the normal manner. In Case 2, multiple openings of the sinus into the atrium were found. No communication existed between the pulmonary veins and the coronary sinus. The atria were in communication by a slit-like opening situated in the position of the ostium primum in the anterior part of the interatrial septum (Fig. 2). Microscopic examination of the atria revealed nothing remarkable except in Case 3, in which the endocardium of the left chamber was somewhat thickened and revealed an excess of elastic tissue as compared with the right side. In the position where the mitral valves would normally be present, there was in each case a semilunar fold of endocardium with

Fig. 1.

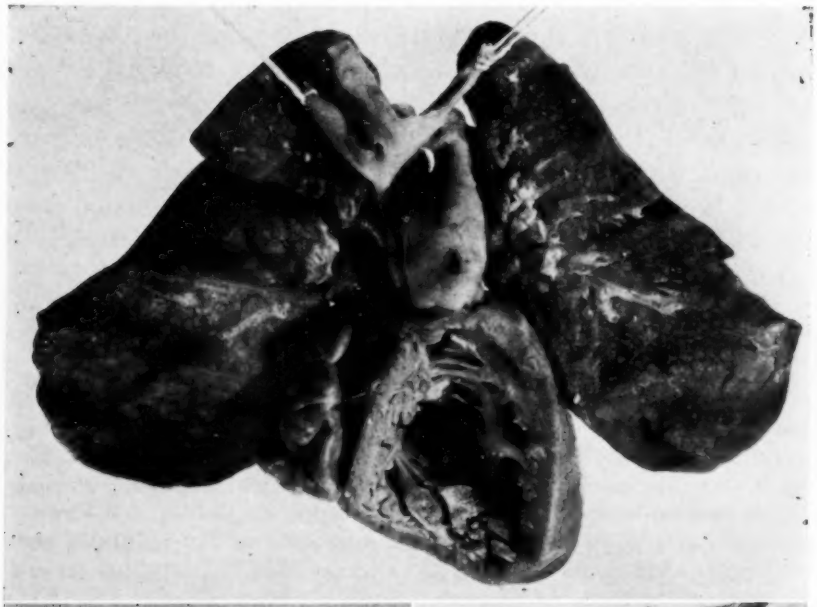

Fig. 2.

Fig. 3.

Fig. 1.—Heart and lungs from Case 1, showing the large, apparently single right ventricle with the large pulmonary trunk and ductus arteriosus and hypoplastic aorta.

Fig. 2.—Left atrium from Case 3, opened to show atresia of mitral valve and interatrial septal defect. A probe is seen passing from the left to the right atrium through the slit in the position of the ostium primum.

Fig. 3.—Posterior view of the heart from Case 2, showing the hypoplastic aorta connected to the large pulmonary artery by a patent ductus arteriosus. The origin of the coronary vessels can be seen.

Fig. 4.

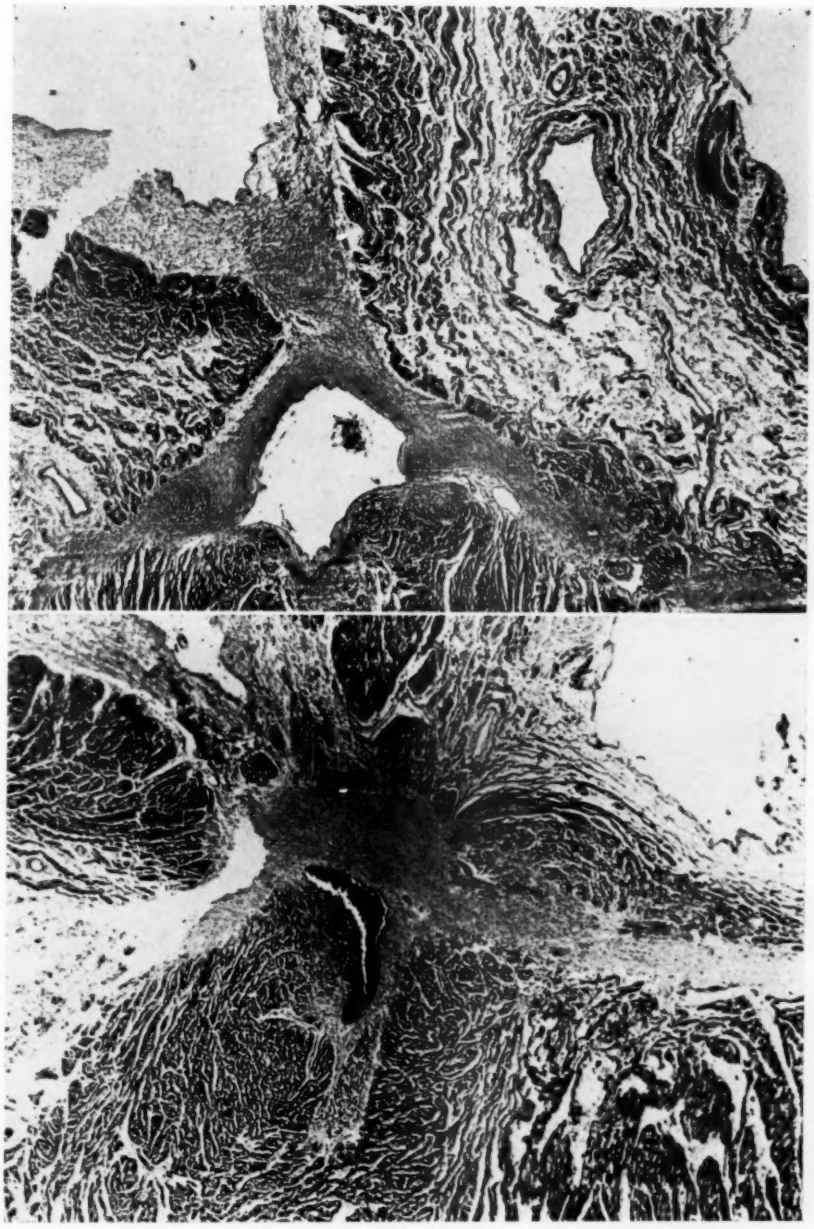

Fig. 5.

Fig. 4.—Case 3. Vestigial left ventricle lying below the annulus fibrosus. The conduction tissue can be seen above and to the right of the annulus fibrosus, and at one point (right lower portion of field) it is beginning to penetrate the fibrous tissue (hematoxylin and eosin, ×16; reduced ¼).

Fig. 5.—Case 2. Vestigial left ventricle containing blood, lying below the annulus fibrosus. The conduction tissue is seen above and to the right of the annulus, and part of the left bundle branch is seen immediately below and to the right of the ventricular cavity (hematoxylin and eosin, ×16; reduced ¼).

no valve cusp formation or opening (Fig. 2). Blood from the atria entered a large right ventricle through a tricuspid valve, which measured 5, 3.5, and 6.5 cm. in the three cases, respectively. The structure of the ventricles was normal except that their walls were thickened. The pulmonic valves were tricuspid. The pulmonary arteries were large and branched in a normal manner to produce the left and right pulmonary arteries (Fig. 1). In each case the ductus arteriosus was widely patent, and the arch of the aorta distal to its opening was within normal limits; the ascending aorta and the arch proximal to the ductus arteriosus was extremely hypoplastic; the great vessels arose in a normal anatomic position proximal to the ductus arteriosus but their blood supply was through the pulmonary artery and ductus arteriosus; and the origin of the aorta was a blind sac in which a rudimentary but correctly oriented aortic valve was seen. The origin of the two coronary arteries in all three cases was in a normal relationship to the valve cusps. These vessels received blood by retrograde flow through the hypoplastic aortas (Figs. 1 and 3). At first sight, the distribution of the coronary arteries appeared to be unusual. When considered in relation to the vestigial left ventricle, they were seen to have an essentially normal pattern (Fig. 9, *Upper and Lower Right*). All the branches were present for the supply of a normally developed left ventricle, but its extremely small size caused their apparently unusual course. The weights and measurements of the three hearts are shown in Table I.

TABLE I

	CASE 1	CASE 2	CASE 3
Age of mother (yr.)	25	33	21
Sex of infant	Male	Male	Female
Onset of cyanosis (hr.)	20	24	72
Time of death (hr.)	30	36	80
Weight of infant (grams)	3,615	2,380	3,100
Heart weight (grams)	16	15	20
Expected heart weight (grams)	21.7	17.9	20.1
Pulmonary valve (cm.)	2.75	2.1	2.25
Tricuspid valve (cm.)	5.00	3.5	6.5
Ostium primum (slit-length) (mm.)	7	8	8
Right ventricular thickness (mm.)			
Right side	5	6	8
Left side	4	4	5
Ductus arteriosus internal diameter (cm.)	0.5	1	1
Pulmonary trunk internal diameter (cm.)	1.1	1	1
Aorta internal diameter (mm.)	1.5	1.5	2

A conventional examination of the heart disclosed no evidence of the left ventricle. Further dissections were performed in order to study the distribution of the conduction tissue distal to the atrioventricular node, and also to search for a vestigial left ventricle. In each case a block of muscle was taken from the upper left wall of the right ventricle and the interatrial septum. It was bounded posteriorly by the entrance of the coronary sinus into the right atrium and anteriorly by the blind origin of the aorta. In Case 3, within the apparently

Fig. 6.

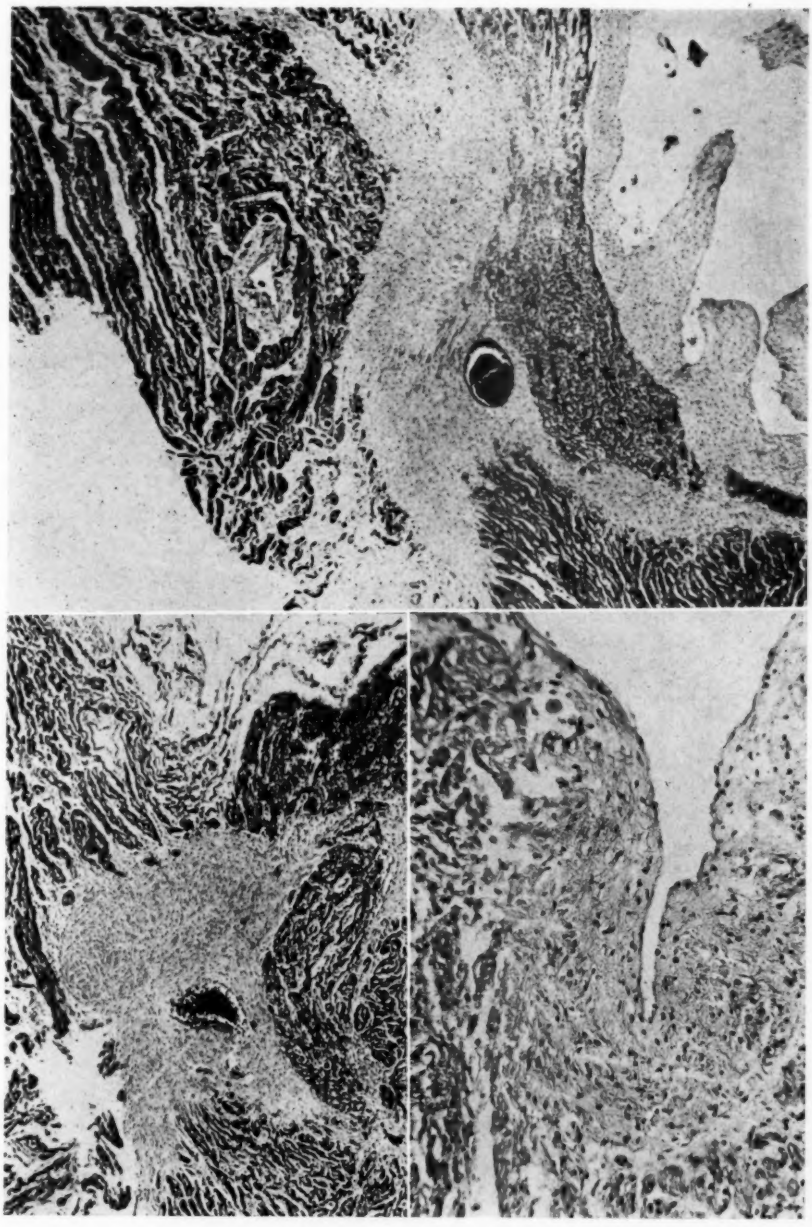

Fig. 7. Fig. 8.

Fig. 6.—Case 1. Vestigial ventricle containing blood. The conduction tissue is to the right, extending both above and below the cavity. Part of the tricuspid valve is seen to the right of the conduction tissue (hematoxylin and eosin, ×16; reduced ¼).

Fig. 7.—Case 1; A section taken anteriorly in the tissue block, showing the left bundle branch passing to the right of the vestigial left ventricle (hematoxylin and eosin, ×16; reduced ¼).

Fig. 8.—Case 3. Lining of vestigial ventricle, showing connective tissue merging into the surrounding cardiac muscle fibers (hematoxylin and eosin, ×100; reduced ¼).

solid muscle of the ventricle, a 2-mm. slit was found immediately inferior to the atretic aortic and mitral valves, which was in the anatomic position of the left ventricle. In Cases 1 and 2, no cavity could be seen on gross examination. In each case, serial sections were made of the block of muscle. In Case 3, the cavity seen on gross examination was found lying just below the annulus fibrosus (Fig. 4). It was lined by flattened cells which had an appearance similar to endothelial cells, and was surrounded by connective tissue merging into the cardiac muscle (Fig. 8). A few erythrocytes were seen lying in the cavity. No elastic tissue could be demonstrated in the wall. In Cases 1 and 2, an apparently similar but smaller space was found on microscopic examination in the same anatomic position as that already described (Figs. 5 and 6).

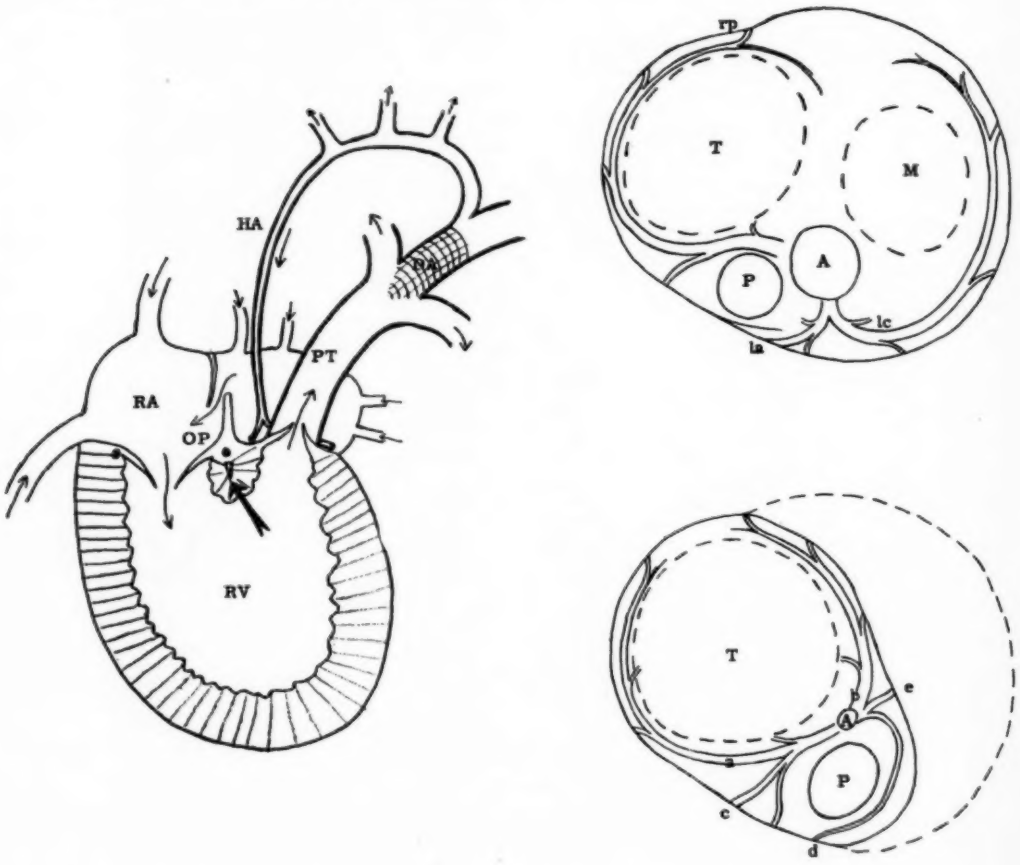

Fig. 9.—*Left:* Composite diagram of the three hearts illustrating the abnormalities. *RV:* Right ventricle. *RA:* Right atrium. *OP:* Interatrial septal defect. *PT:* Pulmonary trunk. *DA:* Ductus arteriosus. *HA:* Hypoplastic aorta. Light arrows indicate direction of blood flow. Heavy arrow indicates vestigial left ventricle. *Upper Right:* Diagram of transverse section of normal heart at level of atrioventricular junction seen from above. *A:* Aorta. *P:* Pulmonary trunk. *M:* Mitral valve. *T:* Tricuspid valve. *1a:* Anterior descending branch of left coronary artery. *1c:* Circumflex branch of left coronary artery. *rp:* Posterior descending branch of right coronary artery. *Lower Right:* View similar to upper right diagram from abnormal cases. Continuous line represents outline of ventricles, showing hypoplastic left side. Interrupted line indicates normal position of left heart margin. Origin of left coronary artery is in a posterior position. *A:* Hypoplastic aorta. *P:* Pulmonary trunk. *T:* Tricuspid valve. *a:* Right coronary artery. *b:* Left circumflex artery. *c:* Anterior descending branch of right coronary artery. *d:* Anterior descending branch of left coronary artery. *e:* Marginal branch of left coronary artery.

Examination of the conduction tissue revealed a normal distribution. The atrioventricular node and bundle of His were found above the annulus fibrosus and to the right, in the posterior part of the blocks examined (Figs. 4, 5, and 6). In the more anterior sections the bundle penetrated through the annulus and divided into two branches. One (the right bundle branch) occupied a position deep beneath the endocardium of the right ventricle and could be followed for a considerable distance (Figs. 5 and 6). The other (the left bundle branch) passed close to the right side of the slit-like vestigial left ventricle and then merged immediately into the main mass of cardiac muscle (Figs. 5 and 7).

DISCUSSION

Death in these cases resulted from cardiac failure. During the period that life was maintained, systemic blood flow was possible by the activity of the large right ventricle in the presence of the widely patent ductus arteriosus. Oxygenated blood from the pulmonary veins must have reached the ventricle by way of the interatrial defect and right atrium. It is interesting to note that at birth the infants experienced no respiratory distress, and cyanosis did not appear for several hours. Once failure developed, however, deterioration was rapid. It seems likely that the mechanism of death was primary myocardial failure brought about by the interplay of several factors. These included the extra work demanded of a single functional ventricle supplying both the systemic and the pulmonic circulation, the restricted blood supply to the myocardium by retrograde flow through the hypoplastic aorta to the coronary arteries, and the inadequate mechanism for oxygenation of the blood.

These hearts were three chambered from the point of view of physiologic function. The left ventricle was in each case vestigial, and the red blood cells seen in the cavity must be assumed to have come from small vascular communications with the myocardium. No doubt existed in our minds that the structure seen in Case 3 represented a vestigial left ventricle. In Cases 1 and 2, in view of the extremely small size of the structures, the question arose as to whether this was a vestigial ventricle or whether it was a large blood vessel. Examination of a number of normal hearts of similar age did not reveal a comparable structure in the same position. In view of the anatomic position of the cavity and the similarity of the appearances in Cases 1 and 2 to those seen in Case 3, we feel that it is reasonable to assume that all three cavities represent vestigial left ventricles. Further evidence for this view was obtained from the study of the distribution of the conduction tissue. The left bundle was in direct relationship to the right side of the vestigial structure, which is its normal relationship to the fully developed left ventricle.

Speculation as to the cause of this deformity is interesting. It would appear that the anomaly must have occurred early in fetal life, when both ventricles were extremely small but when the interventricular septum had developed. The study of the conduction tissue showed an essentially normal distribution of the type found when two ventricles are present. The coronary vascular distribution also showed all the branches to be present which would normally supply the fully developed ventricle. We find ourselves in general agreement with those

workers[4] who have suggested that failure of the mitral valve to develop is the most important single factor in the production of this syndrome. This, in addition to atresia of the aortic opening, must lead to failure of adequate development of the left ventricular cavity.

It is difficult to imagine effective treatment for this condition. The first few hours of life gave little indication of the impending, rapidly fatal myocardial failure. Therefore, diagnosis and preventive measures, even if any could be devised, are made difficult. Surgical intervention, if early diagnosis could be made, seems to offer no real hope in view of the multiplicity of abnormalities.

SUMMARY

Three cases of atresia of the mitral and aortic valves with vestigial left ventricle are presented. The relationship of this condition to cor triloculare biatriatum and to the "hypoplastic left heart syndrome" is discussed. The distribution of the conduction tissue and coronary blood supply is considered. The difficulties of clinical diagnosis and therapy are stressed.

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Experimental and Laboratory Reports

Digitalis Tolerance and Effect of Acetyl-Strophanthidin Upon Serum Potassium of Dogs With Acidosis and Uremia

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Evidence exists that the cardiac glycosides may initiate important shifts in the concentration of potassium (K) in both cellular and extracellular fluid.[1-4] Their administration to normal dogs usually produces slight increases in serum K.[1] Two clinical observations have also suggested a peculiarity of action of this drug in the uremic state. First, digitalization of patients with renal insufficiency sometimes apparently causes serum K to rise significantly, and second, some uremic patients have become intoxicated with relatively modest amounts of digitalis. In an attempt to evaluate these clinical impressions the effects of acetyl-strophanthidin (AS) upon the electrocardiogram and the serum electrolyte pattern of normal dogs were compared with those occurring in dogs made acidotic with ammonium chloride or uremic by bilateral ureteral ligation. Changes in tolerance to AS were also studied in each group. The results suggest that digitalis may induce significant hyperkalemia in the presence of uremia or metabolic acidosis. The results may be explained on the basis of previously reported alterations in permeability of the cell membrane.

MATERIALS AND METHODS

1. *The Determination of Digitalis Tolerance.*—Lown's method of incremental digitalization with AS to the point of ventricular tachycardia was attempted.[5] In his studies with normal dogs, this arrhythmia was attained repeatedly by approximately the same total dosage. In our hands, however, there was a high mortality in such animals since many subsequently developed ventricular fibrillation, even though no further AS was given. Various types of nodal rhythm almost always preceded ventricular tachycardia. The electrocardiogram usually showed complete A-V ("interference") dissociation or nodal tachycardia, and the ventricular complexes often exhibited aberration (Fig. 1). In the latter instance, the focus was considered nodal rather than ventricular if the QRS duration was not increased. Premature ventricular contractions usually appeared about the same time. The appearance of these changes, therefore, was adopted as a safer end point than ventricular tachycardia.

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Supported in part by grants from the National Heart Institute, United States Public Health Service, and the Georgia Heart Association.
Received for publication Aug. 24, 1959.

Light morphine-pentobarbital anesthesia was employed in every study. An initial intravenous dose of 0.6 mg. of AS was followed by 0.3 mg. every 5 minutes until the arrhythmia appeared. In the following experiments, only dogs that could be thus "standardized" with the same total dose three to eight times with a variance of one dosage increment or less were used (about 80 per cent of animals attempted). Standard electrocardiographic leads were monitored continuously on an oscilloscope and recordings were made before each injection of the drug. A total of 151 digitalizations were performed in 29 dogs (9 to 19 kilograms).

2. *NH_4Cl Acidosis.*—A standard experiment was devised in which enough NH_4Cl was given intravenously to cause significant acidosis (as judged by a fall in the serum content of carbon dioxide) with a minimal effect on the electrocardiogram (minor T-wave changes only). A 5.3 per cent solution infused at the rate of 1 mEq. of chloride ion per minute for 60 minutes usually lowered the serum CO_2 to about 15 mEq./L. Twenty-seven infusions were successfully performed in 7 animals whose tolerance to AS had been previously measured in the manner described. Immediately at the end of the infusion the tolerance to AS was again tested.

3. *Uremia.*—Six dogs whose tolerance to AS had been determined were made uremic by the following procedure. A solid nylon suture padded with Ivalon was looped about each ureter and the free ends led through a cannula so placed that its head lay just beneath the skin. The tension of the ureteral snares was maintained by a silver clip attached to the suture ends and could be varied by making a simple skin incision and tightening or loosening the sutures. The degree of nitrogen retention could be roughly controlled by this means. Tolerance to AS was again determined in these animals on 25 occasions at levels of nonprotein nitrogen varying between 60 and 365 mg. per cent.

4. *Biochemical Determinations.*—As a control, the concentrations of Na, Cl, CO_2, and K in venous serum were determined before, during, and after the administration of AS in 18 "standard" digitalizations. The same determinations were made during the 27 infusions of NH_4Cl, and at the point of AS-induced nodal rhythm. In the 6 uremic animals, concentrations of serum electrolytes and nonprotein nitrogen were determined before and after each assay of AS.

RESULTS

Shifts in serum Na, Cl, CO_2, and nonprotein nitrogen after digitalization appeared to be random, unrelated to tolerance to AS, and not to justify statistical analysis. Table I contains the data on serum K obtained from three groups of

TABLE I. STATISTICAL DESCRIPTION OF LEVELS OF SERUM POTASSIUM (MEQ./L.) BEFORE AND AFTER ACETYL-STROPHANTHIDIN-INDUCED NODAL RHYTHM

	STANDARDIZATION		AFTER NH_4Cl			DURING UREMIA		
	CONTROL	NODAL RHYTHM	1. CONTROL	2. ACIDOSIS	3. NODAL RHYTHM	1. CONTROL	2. UREMIA	3. NODAL RHYTHM
Number	18	18	29	27	25	6	26	25
Range	3.4–4.9	3.7–5.4	4.0–5.5	4.0–8.8	4.0–11.0	4.3–4.6	3.1–6.3	4.1–10.2
Mean	4.03	4.24	4.38	5.85	7.39	4.46	4.91	6.19
S.D.±	0.45	0.61	0.61	1.00	1.825	0.27	1.45	2.28
Difference in means = 0.21 t = 1.15 (where t = 2.04 at p = 0.05)			Difference in means 1 and 2 = 1.47 t = 11.74 (where t = 3.46 at p = 0.001) Difference in means 2 and 3 = 1.54 t = 4.10 (where t = 3.46 at p = 0.001)			Difference in means 1 and 2 = 0.45 t = 0.717 (where t = 2.04 at p = 0.05) Difference in means 2 and 3 = 1.28 t = 2.35 (where t = 2.01 at p = 0.05 and t = 2.46 at p = 0.02)		

animals. Two animals with NH_4Cl acidosis did not survive digitalization, and their figures have been excluded. In control animals, serum K tended to remain the same or increased slightly, but in the group this trend was not statistically significant (Table I).

After administration of NH_4Cl the serum content of CO_2 was usually moderately depressed (mean 15.3 ± 4.75 mEq./L.). The rises in serum K were usually slight but consistent (Table I, Fig. 1) and were reflected by T-wave tenting in the electrocardiogram (Fig. 2,*B*). Further increases in serum K after AS in both the acidosis and uremia experiments usually occurred, but were highly variable. Although the effect was usually more marked in the studies with NH_4Cl, the ranges (Table I) and individual experiments (Figs. 1 and 2) indicate that digitalization sometimes produced striking hyperkalemia in both groups but never in normal animals (Table I). In 7 experiments with NH_4Cl alone, serum K was maximal at the end of the infusion, fell abruptly, and then rose slowly (Fig. 1). Continued increase in the serum content of K, therefore, in animals given NH_4Cl and subsequently digitalized could reasonably be attributed to the effects of AS.

The uremic animals did not consistently exhibit hyperkalemia before AS, although significant increases in K were recorded in an occasional experiment (Table I, Fig. 3). Few dogs were anuric, except briefly, and most were probably in negative potassium balance, since anorexia and vomiting occurred frequently. Several showed a decrease in serum K (Figs. 3 and 4). Acidosis was slight as judged by content of CO_2 (mean 18.47 ± 3.37 mEq./L.).

Table II summarizes the dosages of AS necessary to produce nodal rhythm under control conditions and in the same animals after NH_4Cl acidosis or uremia had been produced. In the NH_4Cl group, tolerance was greatly increased (Fig. 4); all animals so included survived the large doses and did not develop ventricular

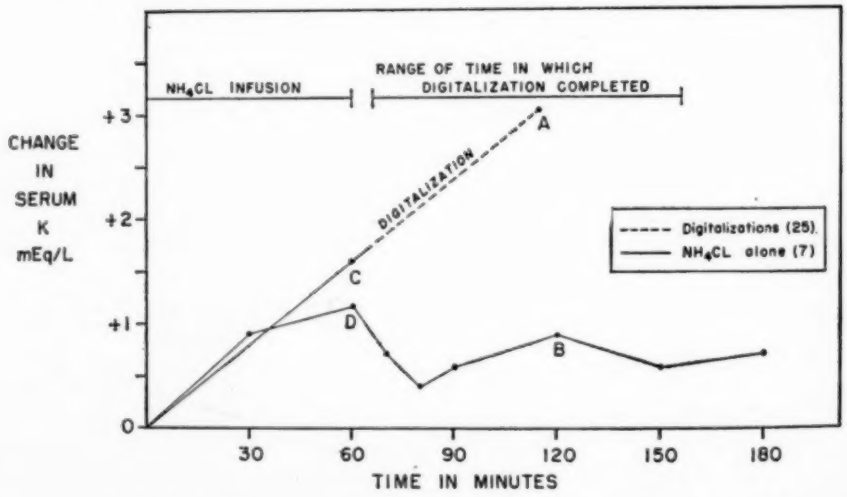

Fig. 1.—Composite curves of changes in serum K after NH_4Cl alone (*lower*) and NH_4Cl followed by digitalization to nodal rhythm. The mean dose for the latter was 4.05 mg. of AS and was completed in a mean time of 55 minutes after the end of infusion of NH_4Cl. In both sets of experiments, NH_4Cl was given at the rate of 1 mEq./min. The difference between the mean changes at points *A* and *B* is highly significant (t = 4.55, t for p of 0.001 = 3.646). The difference between means *C* and *D* is not significant (t = 3.55; t for p of 0.05 = 2.045).

tachycardia. The tolerance of the uremic dogs as a group was not changed but was significantly more variable than that of the controls. These changes in tolerance are related to shifts in serum K (Fig. 3). In no case was a fall in serum K associated with an increase in tolerance to AS. In 5 instances a rise in serum K was associated with a decrease in tolerance to AS, but only once was the latter change greater than one dose increment of AS (0.3 mg.). In these two groups of experiments, therefore, increases in serum K are associated with either no change or an increased tolerance to AS; when a decrease in serum K occurred, there was no change or a fall in tolerance. There was no obvious relationship between the magnitude of the AS-induced rise in K and tolerance to AS; serum K usually rose on digitalization regardless of initial levels or tolerance. Levels of nonprotein nitrogen (Fig. 4) and changes in CO_2 were not directly related to tolerance.

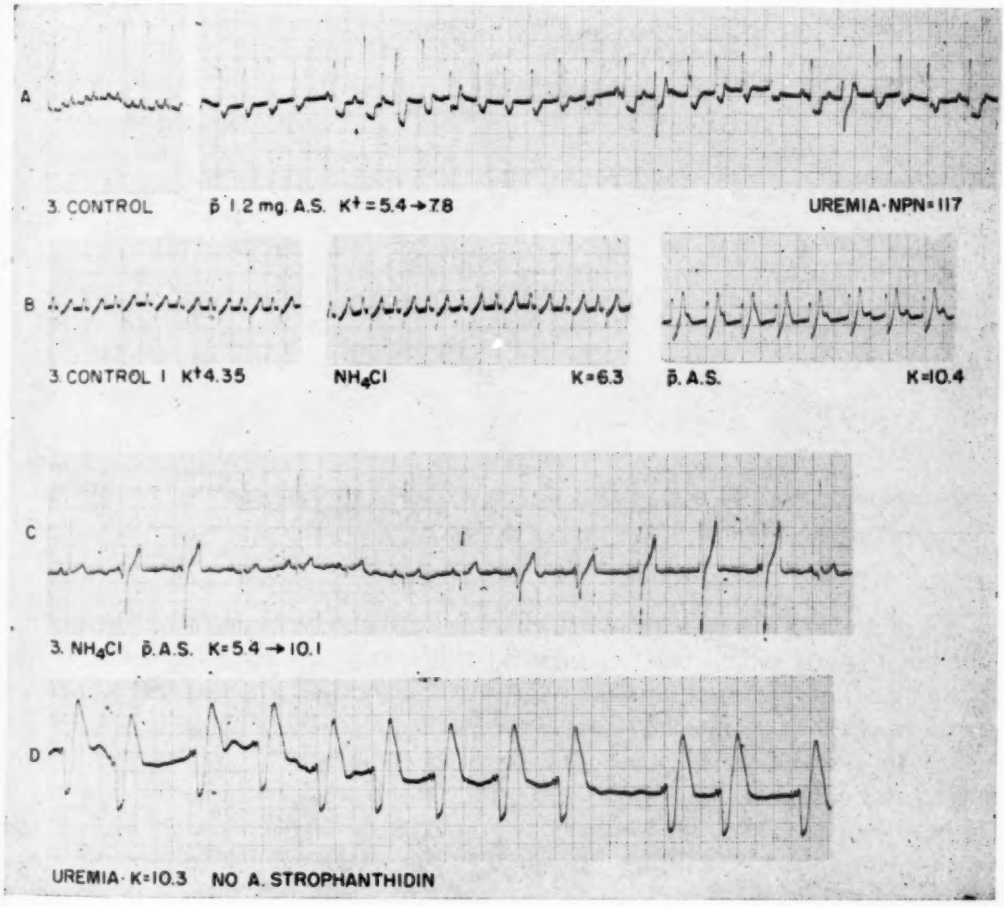

Fig. 2.—*A*, Electrocardiographic end point in a uremic animal. Tracing shows QRS aberrations, nodal rhythm with intermittent A-V dissociation, and ST-T changes compatible with digitalis effect. No definite evidence of hyperkalemia in spite of sudden rise in serum K. *B*, Of 11 experiments in which serum K rose to between 8 and 11 mEq./L. after digitalization, this is the only tracing which suggested hyperkalemia. Nodal rhythm with A-V dissociation is present (after 3.3 mg. of AS). Animal survived. *C* and *D*, Similar levels of serum K in digitalized and nondigitalized animals. In the latter, the severe intraventricular block, giant T waves without S-T intervals, and absent P waves are typical of advanced hyperkalemia. The digitalized animal does not show these changes.

The electrocardiograms with the highest levels of serum K after administration of AS were surprising. In general, they did not differ morphologically from those produced by AS at normal levels of K. After digitalization in 7 NH_4Cl experiments, the levels of serum K ranged from 8 to 11 mEq./L., and in 4 uremic dogs the levels ranged from 8 to 10.2. All 11 animals survived; none showed the disappearance of P waves, bizarre wide QRS complex, and slow idioventricular rhythm progressing to standstill so regularly associated with severe hyperkalemia (Fig. 2). Although ventricular arrhythmias induced by AS might conceivably be difficult to differentiate morphologically from hyperkalemia, it is to be emphasized that digitalization was carried only to nodal rhythm. In contrast, all undigitalized animals with similar levels of serum K which received lethal doses of NH_4Cl or that died in uremia exhibited, as expected, the above-mentioned terminal sequence (Fig. 2).

TABLE II. DOSAGE OF ACETYL-STROPHANTHIDIN (MG.) TO INDUCE NODAL RHYTHM BEFORE AND AFTER PRODUCTION OF NH_4Cl ACIDOSIS OR UREMIA

	NH_4Cl EXPERIMENTS		UREMIA EXPERIMENTS	
	CONTROL	NH_4Cl	CONTROL	UREMIA
Number	40	27	22	25
Range	0.9–2.4	0.6–9.6	0.9–2.4	0.6–3.6
Mean	1.40	4.05	1.20	1.32
S.D.±	0.42	2.29	0.39	0.77
	Variance ratio = 30.57 (VR = 3.01 where p = 0.001) Difference in means = 2.65 t = 7.05 (where t = 3.46 at p = 0.001)		Variance ratio = 3.821 (VR = 2.75 at p = 0.001) Difference in means = 0.12 t = 0.643 (where t = 2.000 at p = 0.05)	

DISCUSSION

An important, perhaps primary, effect of cardiac glycosides is on the permeability of the cell membrane,[6] changes in which can be demonstrated in erythrocytes[3] and in perfused animal hearts.[7] This action appears to block the normal re-entry of K into the depolarized cell and thus to cause a net cellular deficit.[2] This blockade is not an all-or-none phenomenon but can be graded by varying the concentration of the glycoside in the fluid bathing the cell.[3] It is enhanced by lowering and inhibited by raising the concentration of K.[3] The effect is also suggested in intact animals by a rise in the venous and, particularly, the coronary sinus concentration of K after digitalization.[1,8] Others have shown that when a small load of K, insufficient to cause much of a rise in serum K, is infused in dogs, small quantities of AS produce striking rises in serum K and a reversal of the A-V differences for this ion across skeletal and heart muscle beds, which indicates inability of cells in these sites to accept the infused K normally.[4]

Venous serum K rises only slightly when normal animals are rapidly digitalized (about 0.4 mEq./L.).[1] When normal dogs are given a small load of K,

however, AS causes striking rises, sometimes to 10 or 11 mEq./L.[4] These figures resemble those for the maximum levels of K after AS in the NH_4Cl experiments of this study. Indeed, the NH_4Cl experiments described here may be considered somewhat similar; this acid causes an autotransfusion of K ions from the animal's own cells. The active transport mechanism necessary to maintain the normally

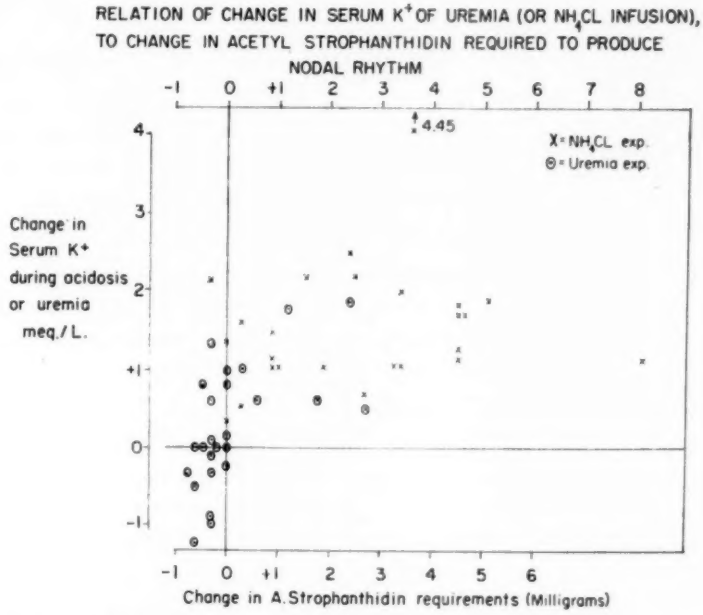
RELATION OF CHANGE IN SERUM K+ OF UREMIA (OR NH4CL INFUSION),
TO CHANGE IN ACETYL STROPHANTHIDIN REQUIRED TO PRODUCE
NODAL RHYTHM
-1 0 +1 2 3 4 5 6 7 8
4.45
X = NH4CL exp.
⊖ = Uremia exp.
Change in Serum K+ during acidosis or uremia meq./L.
4
3
2
+1
0
-1
-1 0 +1 2 3 4 5 6
Change in A. Strophanthidin requirements (Milligrams)

Fig. 3.—Comparison of tolerance to AS and changes in serum K induced by NH_4Cl or uremia. Falls in serum K were associated with no change or decreased tolerance to AS; rises were associated with no changes or increased tolerance.

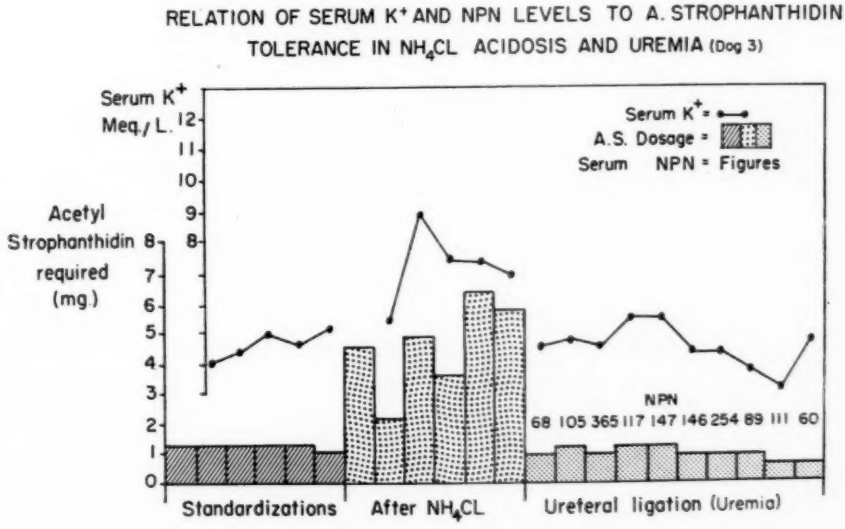

Fig. 4.—A series of digitalizations in a single dog under various conditions. The acute acidosis consistently resulted in higher levels of serum K and greatly increased tolerance to AS. When uremic, AS required to induce toxicity was unchanged or decreased, as were levels of serum K. Levels of nonprotein nitrogen were unrelated to tolerance to AS.

high cellular content of K is allegedly enhanced by a slightly alkaline medium (cells take up K) and inhibited with falls in pH (cells lose K).[9] This probably explains why infusion of NH_4Cl results in rises in serum K.[10] The infusion of the strongly acid solution followed by large amounts of AS appears to have an additive or synergistic effect; the second drug causes a further outpouring of cellular K.

In the uremic dogs the mean content of CO_2 was 18.47 ± 3.37. The moderate acidosis presumably set the stage for further extrusion of K when AS was added. The less marked mean shifts of K after digitalization in these experiments may be related to the biochemical heterogeneity of this group and the chronicity and relative mildness of the acidosis as compared with those of the NH_4Cl experiments.

The changes in tolerance to AS observed in these experiments were along expected lines. The typical electrocardiographic changes of digitalization have been shown to depend on cellular loss of K occasioned by the drug.[7] In the NH_4Cl experiments, larger amounts of AS were apparently required to cause this shift because of the necessity of overcoming a transmembrane K gradient which did not favor extrusion (high serum and presumably low intracellular K). The majority of uremia experiments probably had a quite different type of transmembrane gradient (low or normal intracellular K, low or normal extracellular K); these animals were indeed often intolerant to AS. Clinical examples of intolerance to digitalis are somewhat similar, with total body K depleted and low or normal serum levels.[11] The principal feature of the tolerance studies in this group was their unpredictability. This is not too surprising since the uremia ranged from mild to severe and the group was heterogeneous in other ways. None of the parameters studied clearly explained the changes in tolerance, but the relation to serum K was suggestive (Fig. 3).

Surprisingly little evidence of severe K poisoning was noted electrocardiographically after digitalization, even when serum levels rose sharply (Fig. 2). Milder degrees are more difficult to exclude in the digitalized dog since electrocardiograms in cases of digitalis and K poisoning may have a number of features in common—A-V blocks, nodal rhythm, T-wave peaking, bradycardia, etc.[10] Keyl[12] has pointed out that in normal dogs the strong membrane blockade relative to the re-entry of K invoked by digitalis toxicity is too complete to be overcome even by raising the serum K sharply. It appears possible that the strong AS blockade in these experiments, although enhancing hyperkalemia, at the same time protected the cardiac cells against the high levels of serum K. This hypothesis is supported by other work which indicates that electrocardiographic changes compatible with hyperkalemia in the perfused heart are associated with cellular uptake of K and not external K environment alone.[13]

CONCLUSIONS

1. In an assessment of "digitalis tolerance" with acetyl-strophanthidin (AS), nodal rhythm appeared to be a satisfactory and safer end point than ventricular tachycardia with the dosage schedule employed in these studies.

2. The appearance of nodal rhythm in normal dogs was not consistently accompanied by a rise in serum content of K.

3. In contrast, rises in serum K after similar digitalization in dogs made acidotic with NH_4Cl or by experimental uremia were statistically significant and often dramatic. This hyperkalemia appeared to be an additive or synergistic effect of acidosis and the glycoside, favoring the loss of cellular potassium into the serum.

4. Digitalis (AS) tolerance increased sharply in acute NH_4Cl acidosis, but was not significantly altered in the uremic animals as a group. In the latter, however, tolerance was highly variable (unlike the findings in the control animals) and unpredictable.

5. When increases in tolerance to AS occurred after NH_4Cl acidosis or uremia, the serum K was found to be elevated; decreased tolerance was accompanied by no change or lower serum K. Tolerance was not systematically related to changes in the levels of Na, Cl, CO_2, or nonprotein nitrogen in these experiments.

6. In spite of rises of serum K to levels as high as 9 to 11 mEq./L. after digitalization to nodal rhythm, electrocardiographic effects attributable to hyperkalemia were surprisingly rare.

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Assessment of Mitral Regurgitation by Indicator Dilution: A Modification of the Variance Method of Korner and Shillingford

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In 1955, Korner and Shillingford[1,2] described a new approach to the quantification of valvular regurgitation. They analyzed indicator dilution curves with a circulatory model and found that both the flow and the volume between the sites of injection and collection influenced the dispersion of indicator particles. The dispersion, measured as either the variance or the reciprocal of the slope, could be predicted from a regression equation relating these parameters to forward flow and volume. The addition of valvular incompetence increased the dispersion above the level predicted from the prevailing flow and volume. A component of variance or reciprocal of slope which was related to regurgitation could thus be mathematically isolated and used to quantify regurgitant flow. Since the calculated and measured regurgitant flows agreed closely in the model, and since the alterations of dilution curves in the presence of valvular incompetence are qualitatively similar in man and model, Korner and Shillingford applied the method to patients. Regression equations were derived from dilution curves obtained after injections into peripheral veins or the right side of the heart in persons without valvular incompetence, and the method was applied to patients with valvular heart disease.

In a previous study[3] the variance method was tested in patients with isolated mitral valvular disease in whom the severity of regurgitation was graded by surgical and specific clinical criteria. It was demonstrated that the original regression equation of Korner and Shillingford was not applicable to dilution curves obtained after injections into the left atrium. A new regression equation relating volume and systemic flow to variance was derived from our data. The correlations between the surgical or clinical estimates of the severity of regurgitation

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This work was supported in part by grants from the Greater Boston Chapter of the Massachusetts Heart Association and from the National Heart Institute, National Institutes of Health, U. S. Public Health Service (H-442 [C9]).

Received for publication Oct. 26, 1959.

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and the results of the variance method indicated that mitral regurgitation determinably alters the variance of dilution curves independently of the effects of systemic flow and the estimated volume. Thus, the Korner and Shillingford method was validated in man: the method graded the severity of mitral regurgitation in a given patient with reference to a group. However, the calculated numerical values were, in most patients, gross overestimates of regurgitant flow.

In the original description and subsequent applications[2-4] of the variance method the measure of flow is the cardiac output, calculated from the indicator dilution curve as described by Hamilton,[5] and the volume estimate is the "central" volume calculated as the product of mean circulation time and cardiac output.[6] Since the parameter being treated is variance, the volume estimate used should be the entire volume which influences variance, and should include no volume which does not influence the variance. It is apparent that only volume with which recovered indicator is mixed can influence the variance. Meier and Zierler[7] have demonstrated that the product of mean circulation time and cardiac output is usually neither a true central volume nor the volume between injection and collection sites, but is the volume of all temporally equivalent pathways between the sites of injection and collection. Thus, the "central" volume may be considered to have two components. The first consists of the volume between the injection site and the specific collection site: it is the volume with which the recovered indicator can mix. With left atrial injections, this component is anatomically related to the volumes of the left atrium, left ventricle, and the efferent arterial pathway to the collection site. The second component is a peripheral, temporally equivalent, arterial component of indeterminate size which is not traversed by the sampled indicator. Both the second component and that fraction of the first component in which indicator has not actually mixed affect the appearance time and, hence, the mean circulation time and the "central" volume, but cannot influence the variance of the sampled curve. For this reason, with or without stenotic or incompetent valves, the calculated "central" volume is an overestimate of the volume which influences the variance. As increasingly severe mitral regurgitation is studied, the volume with which indicator has mixed represents an increasingly greater fraction of the calculated "central" volume, and the latter is, therefore, a relatively smaller overestimate of the desired volume. The equation for predicting the variance expected in the absence of regurgitation is derived from normal subjects or those with stenotic lesions only, in whom the volume term is a relatively greater overestimate of the volume which affects the sampled curve. It follows that, as more severe degrees of mitral regurgitation are studied, the expected variance will be increasingly underestimated, and regurgitant flow increasingly overestimated.

It is clear that the variance method requires an estimate of volume which, like variance, reflects mixing of the sampled indicator. In 1951, Newman and associates[8] described two volumes based on the disappearance slope and related to mixing. The first of these, which was called the slope volume, was used to estimate the volume of the largest in a series of chambers. The second, the "resid-

ual" volume,* was suggested as a basis for estimating the end-systolic volume of a chamber. Both of these estimates of volume satisfy the afore-mentioned criteria, and either should be more appropriate than the "central" volume for use with the variance method.

The present report deals with a modification of the variance method based on the use of the "residual" volume. It should be recognized that the "residual" volume cannot be equated with the residual of any single chamber when multiple chambers are traversed by indicator. The "residual" volume is, in the presence of mitral regurgitation, a complex function of the volumes of the left atrium, the left ventricle, and the regurgitant bolus. However, rather than introduce a new name, the term "residual" volume is retained with the explicit understanding that it refers to a volume aggregate which behaves as a virtual single volume from which indicator is being washed. The important feature is that variance and slope, or "residual" volume, are functions of the volume in which indicator has mixed.

MATERIAL AND METHODS

The 70 patients are those studied previously.[3] The identifying study numbers are the same as in the previous report. Thirty dilution curves from 25 patients without valvular incompetence provided the data (Table I, *A* and *B*) from which a regression equation was derived. The second group, to whom the modified variance method was applied (Table I, *B* and *C*), contained 5 subjects without physiologically evident valvular disease, and 57 patients with either mitral stenosis or mitral regurgitation, or both. The patients have been classified by two systems. In the first, the categories as determined by the surgeon at the time of operation were: pure mitral stenosis (MS), mitral stenosis and regurgitation with the former predominating (MSmr), combined stenosis and regurgitation with predominant regurgitation (MRms), and essentially pure mitral regurgitation (MR). In the second system the severity of mitral regurgitation was graded on a scale of 1-10 by a combination of clinical and surgical criteria.[3]

All patients were studied by transdorsal puncture of the left atrium[10] with 2 needles, through one of which a polyethylene catheter was passed into the left ventricle. Pressures were measured with strain gauge manometers and were recorded on a direct-writing oscillograph. Mitral diastolic valvular areas were computed according to the Gorlins' hydraulic formula,[11] using a discharge coefficient of 1.0, as empirically determined in this laboratory. The valvular areas drawn by the surgeons were measured in square centimeters with a planimeter. Indicator dilution curves were obtained from the brachial artery with either of two techniques after injection of 4 to 5 mg. of Evans blue dye rapidly into the left atrium from a calibrated pipette.[12] With the first technique, blood was drawn from a brachial artery at a constant rate of 0.7 ml. per second through 40 cm. of polyethylene tubing (internal diameter, 1.13 mm.) and through a cuvette densitometer,[13] the output of which was recorded on the oscillograph. These curves were calibrated with an integrated sample.[14] With the second technique, arterial blood flowed from a cannula at a rate of 1 to 2 ml. per second through 30 cm. of polyethylene tubing (internal diameter, 3 mm.) into heparinized test tubes mounted on a rotating disc. Funnels in the test tubes permitted continuous collection without spillage between samples. The complete cycle of the 24 tubes could be regulated to give a filling period of 1.25 to 2.00 sec. per tube. The characteristics of the first sampling system satisfy, but those of the second system often failed to satisfy, the "figure of merit" for catheter sampling derived by Sherman and associates.[15] However, there was no systematic difference between the estimates of regurgitation from curves obtained with either method within any category of patients. Concentrations of dye in plasma were determined in a spectrophotometer (Beckman model DU)

*Dr. S. W. Stein of this laboratory has shown that the "residual" volume plus one half of the ejection volume equals the slope volume for all combinations of injection and collection sites.[9]

at a wave length of 625 mμ. All dilution curves were plotted semilogarithmically and concentrations extrapolated to 1 per cent of peak value. Systemic flow was calculated according to the method of Hamilton,[5] and "central" volume was calculated as the product of systemic flow and mean circulation time.[6] The "residual" volume was calculated from the following equation, described by Newman and associates[8]:

$$\text{Slope} = R \cdot \log_e \left(\frac{V_R}{V_E + V_R} \right),$$

where slope = change in $\log_e$ concentration per minute during exponential decay; R = heart rate in beats per minute; V_E = stroke volume in liters; V_R = "residual" volume in liters.

The variance of each dilution curve was calculated by the standard statistical formula used by Korner and Shillingford.[2] A regression equation was derived from the data of Group I, using standard mathematical techniques.[16] The variance expected for each curve on the basis of the known prevailing systemic flow and "residual" volume was determined using this equation. The ratio "p" of the expected variance to the observed variance was used to compute regurgitant flow by the equation:

$$\text{Regurgitant Flow} = \frac{\text{Systemic Flow } (1-\text{"p"})}{\text{"p"}}.$$

RESULTS

The data from the first group of patients are given in Table I, *A* and *B*. The regression equation derived from these data is:

$$\log EV_x = 3.1735 - 1.842 \log Q_F + 1.426 \log V_R,$$

where EV_x = the variance expected for the prevailing systemic flow and "residual" volume; Q_F is the systemic flow in liters per minute; and V_R is the "residual" volume in liters. The regression function removed 93 per cent of the sum of squares of the dependent variate.

The data shown in Table I, *B* and *C* were obtained from the second group of patients. Regurgitant flow (Fig. 1) had a moderate correlation with the severity of mitral regurgitation as estimated by the surgical scale ($r = +0.77$) and by the clinical scale ($r = +0.72$). The mean calculated regurgitant flow was 0.4 L. per minute in the group of patients with no regurgitation at operation, and 5.3 L. per minute in the group considered to have essentially pure and severe mitral regurgitation. The absolute values are appropriate for inclusion as part of mitral diastolic flow in the computation of mitral diastolic area. However, the severity of mitral regurgitation is defined by the variance method as the relationship of the probability of regurgitant flow to the probability of systemic flow. The hemodynamic expression of severity by this method, therefore, is the ratio of regurgitant to systemic flow (Q_R/Q_F). This is the datum most amenable to comparison with surgical or clinical classifications. This hemodynamic index of severity (Fig. 2) had a high correlation with the surgical ($r = +0.80$) and the clinical ($r = +0.78$) estimates of severity. Exclusion of the patients whose data were used to derive the regression equation altered these correlations only slightly. The mean values of this ratio were 0.11 for the group without regurgitation at surgery and 1.06 for the group with essentially pure regurgitation.

These results again demonstrate that, in the presence of mitral regurgitation, a determinable portion of variance, which is not predicted from the flow

TABLE I. DATA FROM PATIENTS WITHOUT VALVULAR INCOMPETENCE (PARTS *A* AND *B*) AND PATIENTS WITH ISOLATED MITRAL VALVULAR DISEASE (PARTS *B* AND *C*)

NUMBER	PHYSIOLOGIC DIAGNOSIS	CLASSIFICATION		SYSTEMIC FLOW (L./MIN.)	"RESIDUAL" VOLUME (L./MIN.)	OBSERVED VARIANCE	EXPECTED VARIANCE	ESTIMATED REGURGITANT FLOW (L./MIN.)
		SURGICAL	CLINICAL					
				A.				
56	AS			9.62	0.29	3.30	——	——
73	AS			6.51	0.19	4.88	——	——
79	AS–MS			7.74	0.20	3.23	——	——
81	AS–MS			7.34	0.17	3.36	——	——
14A	AS			4.83	0.09	3.74	——	——
14A	AS			3.61	0.14	7.25	——	——
34A	AS			8.20	0.15	2.31	——	——
37A	AS			6.55	0.15	2.97	——	——
46A	AS			5.40	0.10	2.27	——	——
				B.				
121	N	N		5.82	0.18	5.84	4.97	1.0
122	N	N		9.52	0.21	2.41	2.41	0.0
130	N	N		3.96	0.11	6.31	5.28	0.8
39A	N	N		10.03	0.17	1.90	1.64	1.6
41A	N	N		6.05	0.10	1.79	2.12	−0.9
57	MS	O		5.67	0.41	20.69	16.93	1.3
71	NO*	O		6.07	0.39	16.53	14.00	1.1
71	NO	O		6.99	0.31	10.66	7.92	2.4
88	MS	O		3.78	0.17	9.81	10.03	−0.1
90	MS	O		7.10	0.21	3.99	4.29	−0.6
91	NO	O		4.41	0.22	13.00	11.11	0.7
92	MS	O		4.76	0.17	8.07	6.43	0.9
99	MS	O		3.09	0.15	12.51	11.89	0.1
99	MS	O		3.24	0.17	14.92	13.67	0.3
107	MS	O		3.52	0.13	7.08	8.18	−0.5
107	MS	O		3.19	0.06	3.04	3.49	−0.4
110	MS	O		3.53	0.08	3.69	4.13	−0.4
126	NO	O		7.65	0.18	3.23	3.12	0.3
127	MS	O		5.29	0.12	3.46	3.45	0.0
127	MS	O		8.00	0.17	2.29	2.51	−0.7
32A	MS	O		6.23	0.12	1.99	2.55	−1.3
				C.				
31	MR		6	4.20	0.58	127.80	48.29	6.9
32	MRms		5	3.04	0.56	134.80	83.29	1.9
38	MR		6.3	7.07	1.16	88.38	50.21	5.4
43	MSmr		3	4.02	0.27	20.06	17.40	0.6
44	MSmr		3	7.29	0.44	13.59	11.85	1.1
55	MRms		6	6.60	0.92	65.66	40.93	4.0
60	NO		1.3	6.62	0.24	8.11	5.88	2.5
61	MS		0	6.03	0.47	26.36	18.81	2.4
63	MS		1	4.67	0.30	17.79	15.96	0.5
64	MRms		8	4.59	1.28	230.90	101.90	5.9

NO: No operation.

and the volume estimate used, permits physiologic estimation of the severity of the lesion.

Comparison between the "residual" volume and "central" volume variance methods[3] reveals marked differences in the estimates of regurgitant flow in the same patients. In each group of patients the mean calculated regurgitant flow was lower with the former than with the latter method. The most striking differences were in the group with essentially pure regurgitation, with averages of 5.3 and 16.7 L. per minute and maximal values of 6.9 and 20.6 L. per minute, respectively.

TABLE I. DATA FROM PATIENTS WITHOUT VALVULAR INCOMPETENCE (PARTS *A* AND *B*) AND PATIENTS WITH ISOLATED MITRAL VALVULAR DISEASE (PARTS *B* AND *C*)—Cont'd

NUMBER	CLASSIFICATION		SYSTEMIC FLOW (L./MIN.)	"RESIDUAL" VOLUME (L./MIN.)	OBSERVED VARIANCE	EXPECTED VARIANCE	ESTIMATED REGURGITANT FLOW (L./MIN.)
	SURGICAL	CLINICAL					
74	MRms	6	5.36	0.52	39.17	26.25	2.6
75	MS	3	6.02	0.24	9.28	7.24	1.7
80	MR	8.8	3.25	1.14	369.60	204.80	2.7
83	MS	3	6.61	0.25	7.19	6.51	0.7
84	MR	8.8	4.85	1.82	442.00	191.10	6.4
85	MSmr	1	6.40	0.38	14.03	12.42	0.8
93	MS	2	5.07	0.23	10.19	8.94	0.7
93	MS	2	6.69	0.22	6.83	5.33	1.9
98	MSmr	2	3.99	0.28	20.13	19.35	0.2
104	NO	3.8	4.20	0.25	14.24	15.02	−0.2
105	NO	1.3	5.31	0.15	4.05	4.47	−0.1
106	MSmr	4	4.93	0.46	30.81	25.68	1.0
108	MSmr	1	2.61	0.19	19.02	23.86	−0.5
111	MSmr	3	4.93	0.23	8.52	9.17	−0.4
112	MR	6.3	6.87	0.94	69.51	39.18	5.3
115	NO	1.3	6.36	0.32	10.51	9.59	0.6
115	NO	1.3	4.78	0.25	12.43	11.76	0.2
117	MRms	5	4.46	0.68	88.80	54.31	2.8
119	MS	1	3.41	0.22	15.97	18.08	−0.4
124	MRms	6.3	2.80	0.55	146.50	95.31	1.5
140	NO	2.5	6.30	0.51	24.10	19.01	1.7
141	MS	0	5.20	0.29	12.53	10.48	1.0
141	MS	0	4.13	0.29	18.70	14.79	1.1
12A	NO	1.3	6.96	0.54	26.70	17.55	3.2
28A	NO	1.3	4.64	0.10	2.84	3.26	−0.6
142	MSmr	3	3.63	0.25	21.94	18.65	0.6
142	MSmr	3	5.34	0.49	28.36	24.70	0.7
143	MSmr	3	4.03	0.29	21.55	19.94	0.4
146	NO	1.3	4.79	0.20	8.24	8.21	0.0
148	MSmr	2	4.52	0.16	7.01	6.62	0.4
150	NO	1.3	1.97	0.09	10.02	13.09	−0.4
150	NO	1.3	2.32	0.10	8.51	11.20	−0.6
152	MS	2	5.02	0.28	14.42	12.68	0.7
154	MS	3	3.32	0.19	13.40	15.08	−0.4
157	NO	1.3	5.13	0.19	5.23	6.80	−1.2
158	MSmr	2	3.22	0.31	34.03	33.00	0.1
158	MSmr	2	2.85	0.28	34.64	35.21	0.0
159	NO	5	8.64	0.55	16.42	11.91	3.3
159	NO	5	10.73	0.51	10.70	7.21	5.2
161	NO	0	2.65	0.16	15.50	18.01	−0.4
162	NO	0	2.34	0.13	17.05	20.23	−0.4
162	NO	0	2.66	0.15	11.74	13.79	−0.4
163	NO	6.3	4.39	0.79	112.10	70.25	2.6

TABLE II. MITRAL DIASTOLIC AREA AS DETERMINED BY CALCULATION FROM HEMODYNAMIC DATA AND BY PALPATION AT OPERATION

NUMBER	MITRAL VALVULAR AREAS (CM.²)		
	"CENTRAL" VOLUME METHOD	"RESIDUAL" VOLUME METHOD	SURGEONS' ESTIMATE
43	1.10	0.78	0.7
44	3.12	1.86	0.9
57	1.55	1.71	1.3
61	1.10	1.48	0.7
63	1.95	1.02	1.0
64	3.01	1.51	0.9
71*	2.40	2.80	3.0
71*	2.50	3.40	3.0
75	1.04	1.33	0.8
83*	1.36	1.15	0.9
85	3.05	1.48	1.0
88	0.60	0.60	0.6
90	1.28	1.23	1.3
92	0.92	1.09	0.7
93*	2.59	2.55	2.8
98	1.10	0.60	0.6
99	0.98	1.03	1.2
99	1.03	1.12	1.2
106*	2.20	1.20	1.3
107	0.68	0.57	0.6
107	0.52	0.52	0.6
108	1.02	0.50	0.6
110*	1.85	1.76	2.6
111	1.16	0.75	0.8
119	1.64	0.82	1.3
127*	4.47	3.48	3.6
141*	1.51	1.62	1.3
141*	1.51	1.36	1.3
32A	1.08	0.80	0.7

*Postoperative estimates of mitral valvular area compared with postoperative catheterization results.

TABLE III. DATA FROM 5 PATIENTS WITH SEVERE MITRAL REGURGITATION

NUMBER	MEAN MITRAL DIASTOLIC GRADIENT (MM. Hg)	DIASTOLIC FILLING PERIOD (SEC./MIN.)	REGURGITANT FLOWS		
			THEORETICAL MAXIMUM	"CENTRAL" VOLUME METHOD (L./MIN.)	"RESIDUAL" VOLUME METHOD (L./MIN.)
31	2.9	31.8	7.8	11.4	6.9
38	4.1	27.7	5.4	15.0	5.4
80	2.3	30.0	6.8	17 1	2.7
84	4.0	29.2	8.0	19.4	6.4
112	3.2	29.4	4.8	20.6	5.3

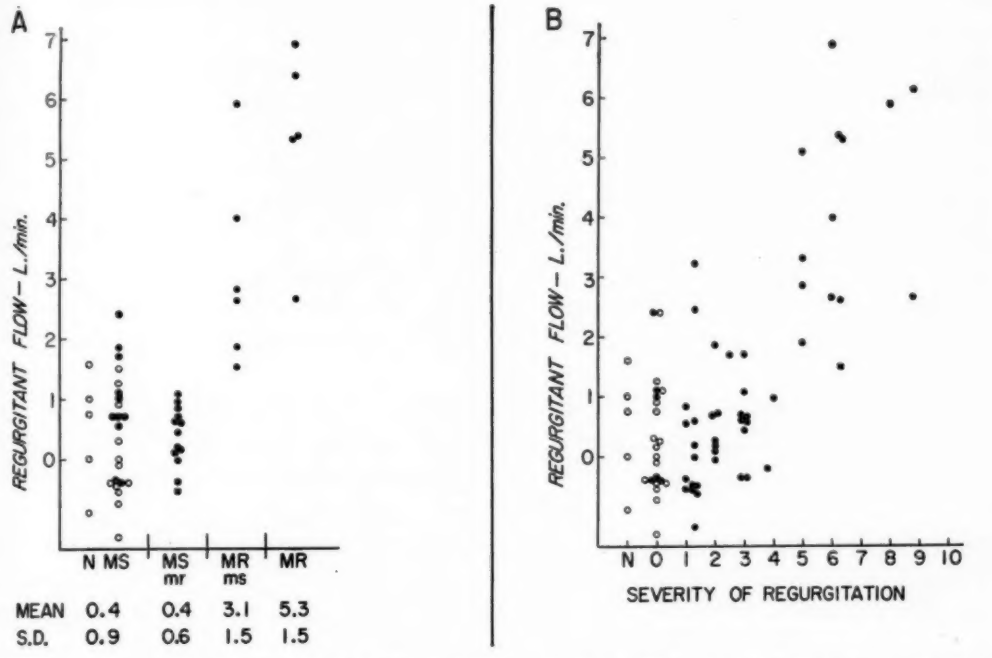

Fig. 1.—Regurgitant flow plotted (*A*) against the surgical and (*B*) against the clinical classification of mitral valvular disease. The correlation coefficients are +0.77 (*A*) and +0.72 (*B*). When the patients whose data were used in deriving the regression equation (*open circles*) are excluded, the correlation coefficients are +0.73 (*A*) and +0.67 (*B*).

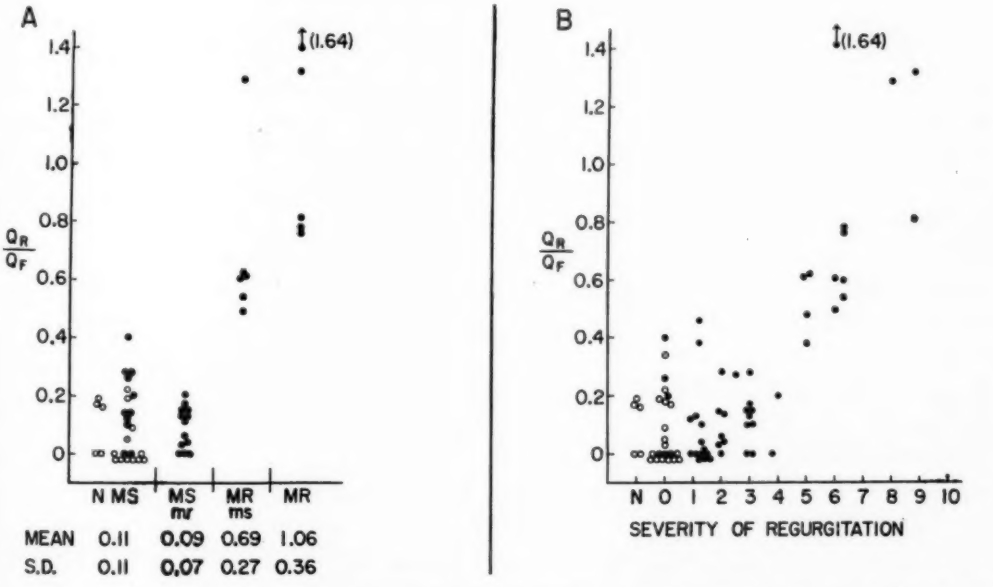

Fig. 2.—Ratio of regurgitant to systemic flow (Q_R/Q_F) plotted (*A*) against the surgical and (*B*) against the clinical classification of mitral valvular disease. The correlation coefficients are +0.80 (*A*) and +0.73 (*B*). When the patients whose data were used in deriving the regression equation (*open circles*) are excluded, the correlation coefficients are +0.78 (*A*) and +0.78 (*B*).

The methods have been evaluated by comparing the calculated mitral diastolic areas with the planimetrically measured surgeons' diagrams. The group available for this analysis consisted largely of patients with no or with mild mitral incompetence. Total mitral diastolic flow was defined, first, as the sum of systemic flow and the regurgitant flow calculated from the "central" volume variance method, and, secondly, as the systemic flow plus the regurgitant flow defined by the present method. The respective calculated areas and the surgeons' estimates for each of 29 studies are shown in Table II and Fig. 3. The valvular areas (*A*) based on data from the "central" volume variance method were frequently gross overestimates. Conversely, the valvular areas (*B*) based on data from the "residual" volume variance method had a very high correlation ($r = +0.91$) with the surgeons' estimates.

The physiologic data were used in another way to evaluate the accuracy of the method. An average effective area of 5 cm.^{2} has been measured by one of us (R. A. C.) in the intact mitral valves of 15 fresh hearts obtained post mortem from patients with congestive heart failure, cardiomegaly, and no rheumatic heart disease. If 5 cm.^{2} is considered the maximal diastolic valvular area for the 5 patients with essentially pure mitral regurgitation, knowledge of the mitral diastolic pressure gradient and the diastolic filling period permits calculation of the maximal diastolic flow. Subtraction of the systemic flow yields the theoretical maximal regurgitant flow which could have occurred under the conditions of study. The data for these computations and the results are given in Table III. The regurgitant flows calculated with the "residual" volume variance method agreed closely with the theoretical maxima, whereas those obtained with the "central" volume method were much larger.

Thus, in the presence of mild or of severe mitral regurgitation, the "residual" volume variance method gave empirically correct estimates of regurgitant flow.

The reproducibility of the method was tested in 12 patients who had two determinations 10 to 56 minutes apart. In 4 patients, calculated regurgitant flow decreased slightly from an initially negative value. In one patient, a very small, regurgitant flow was succeeded by a small negative value. In the other 7 patients, positive regurgitant flows were calculated on each of the two determinations. For these 14 observations, the mean ratio of regurgitant to systemic flow was 0.202, the mean difference between paired determinations was 0.087, and the standard error of an observation was 0.069. The coefficient of variation of measurements of regurgitant flow was 34 per cent in this small sample. If the severity of regurgitation were known to be constant, this would be an estimate of the random error of the method. Conversely, if random error could be excluded, this would be an estimate of the variability of the severity of the lesion. However, random error, including errors of measurement of timed concentration and the small variation in the dependent variate unaccounted for by the regression equation, is, of course, present and responsible for the physiologically absurd negative values. If the assumption is warranted that regurgitation is absent or negligible in the 5 patients whose ratios of regurgitant to systemic flow were negative or very small, then variability of severity is an improbable cause of differences between these paired determinations. Then, the coefficient of vari-

ation in this sample may be used to estimate random error. The mean value of the ratio in these 5 patients was −0.083, the mean difference between paired measurements was 0.031, and the standard error of an observation was 0.032. The coefficient of variation of a measurement was 39 per cent. These data suggest that differences in the ratio of regurgitant to systemic flow in the patients with mitral regurgitation were consistent with random error, and that the severity of regurgitation remained relatively constant under the conditions of study.

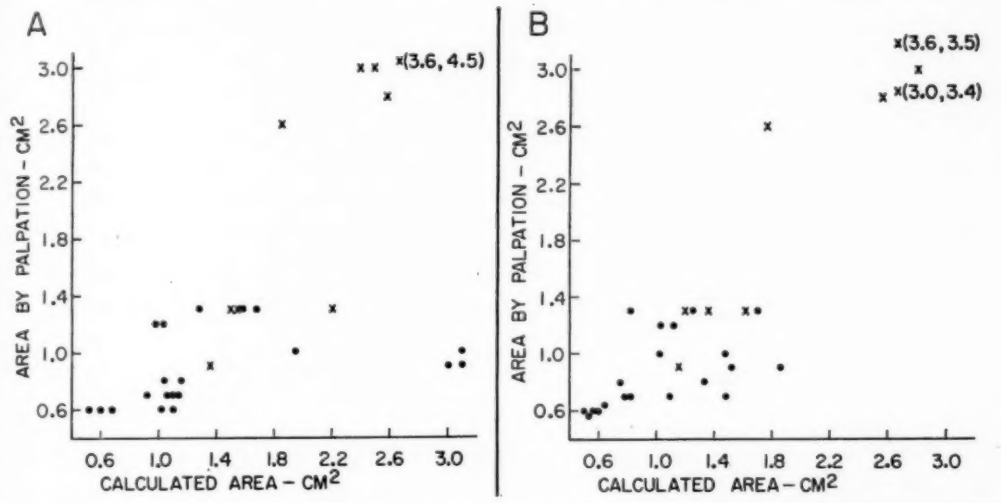

Fig. 3.—Calculated mitral diastolic area plotted against the area estimated by the surgeon. The regurgitant flow calculated with the "central" volume (*A*) and with the "residual" volume (*B*) variance method has been included in the mitral diastolic flow. The correlation coefficients are +0.67 (*A*) and +0.91 (*B*).

DISCUSSION

The parameters of indicator dilution curves are defined by the flows and by the volumes in which indicator mixes between the sites of injection and collection.[17] The increased variance of a dilution curve in a given patient with mitral regurgitation may be contributed to not only by the backflow but also by a decrease in systemic flow or by an increase in the mixing volume. Either of the latter two changes produces a proportional prolongation of all time components and lowers the peak concentration.[1,18] However, mitral regurgitation, with forward flow and chamber volume held constant, has been shown in a model to produce a unique curve distortion consisting of an earlier appearance time, a lower peak concentration, and a disproportionate prolongation of the disappearance slope without a change in the mean circulation time.[1] This distortion, which cannot be completely simulated by changes in forward flow or volume alone, results in part from an increase in mixing volume due to repeated reexposure of indicator to the end-diastolic volume of the atrium.[19] That such an increase in mixing volume occurs *pari passu* with the presence of backflow has been shown experimentally in this laboratory,[19] and mathematically by McClure and associates,[17] who demonstrated that the effect of regurgitation is in part that of a mixing volume and in part that of a flow.

The aim of the variance method is to account for the effects of forward flow and of mixing volume, including the component of augmented mixing volume that is a consequence of regurgitation, and, thereby, to isolate the behavior or the regurgitant bolus as a flow. In the absence of regurgitation, variance has been predicted from a knowledge of forward flow and of the "residual" volume. Since systemic flow is accurately estimated when regurgitation is present,[1] full correction for the influence of forward flow is accomplished in this situation. If the "residual" volume is as successful a representative of the mixing volume in the presence of mitral regurgitation as in its absence, any discrepancy between predicted and observed variance must be a function of the regurgitant flow. Should the "residual" volume be less representative of the mixing volume in the presence of mitral regurgitation, values obtained for regurgitant flow will be malestimates.

The present study demonstrates that estimates of regurgitant flow by the "residual" volume variance method are empirically correct by criteria applicable to clinical mitral regurgitation. Proof of the validity of the estimates and of the method must await comparison with direct methods not yet developed for use in man.

SUMMARY

Five patients with normal mitral valves and 57 patients with isolated mitral valvular disease, in whom the severity of regurgitation was clinically and surgically estimated, were studied by catheterization of the left side of the heart and by indicator dilution curves obtained after injection into the left atrium. The variance method of Korner and Shillingford was modified to include the "residual" volume as an estimate of the mixing volume. This method was applied to data from 74 dilution curves.

The physiologic index of severity, the ratio of regurgitant to systemic flow, correlated well with the clinical and surgical estimates of severity, and varied relatively little in 7 patients with regurgitation in whom two measurements were made.

The mean calculated regurgitant flow was 0.4 L. per minute in the group with pure mitral stenosis at operation and 5.3 L. per minute in the group with pure and severe mitral regurgitation. The calculated regurgitant flows permitted substantially correct estimates of mitral diastolic area and agreed well with predictions of regurgitant flow based on physiologic and anatomic data.

We are indebted to Dr. Lawrence B. Ellis for his interest and helpful criticism. Miss Felicitas Honegger and Miss Mary Collins, R. N., have rendered invaluable technical assistance.

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The Value of Injections of Dye Into the Left Heart in the Study of Mitral and Aortic Valvular Disease by Catheterization of the Left Heart

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Arterial dilution curves have been recorded after injections of dye into the chambers of the left heart during the study of patients with mitral and aortic valvular disease by catheterization of the left heart. Besides providing a measure of cardiac output, these curves give information about valvular regurgitation, and will disclose even a small left-to-right intracardiac shunt. The present study is an evaluation of the extent to which such curves can be used to measure valvular regurgitation, and a comparison between their value and that of the more familiar arterial curves recorded after injection of dye into the pulmonary artery. Thirty-three curves recorded after injection of dye into the left heart of 29 patients have been analyzed; in 22 of these patients the right heart was catheterized simultaneously, and an arterial curve was recorded after injection into the pulmonary artery within 5 minutes of the injection into the left heart.

Prolongation of the downslope in arterial dilution curves recorded after injections of dye into the pulmonary artery was described in patients with valvular regurgitation by Korner and Shillingford.[1] On the assumption that the shape of the dye curve was determined by the three variables, flow, volume, and regurgitation, these authors proposed methods for the calculation of regurgitant flow from dilution curves, and applied them to patients with heart disease.[1,2] Recent studies in the same laboratory[3] suggest that other variables are probably important in many patients with valvular heart disease, and provide an explanation for the discrepancy sometimes noted between the regurgitant flow calculated by these methods and the severity of regurgitation judged by other criteria.[4] Moreover, the calculations are laborious, and simpler methods of analyzing the dilution curves obtained after injections into the pulmonary artery have proved of equal clinical value.[5,6] Dilution curves obtained after injections of dye into

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Supported in part by Grant H-226 from the National Heart Institute.

Received for publication Jan. 15, 1960.

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the left heart are changed in a similar way by valvular regurgitation,[7] but no study is available comparing the clinical value of injections made into the left heart with those made into the pulmonary artery.

Dilution curves recorded in different laboratories cannot always be compared. The shape of a recorded curve differs from that occurring at the point of sampling by some degree of distortion imposed both by the process of sampling blood[8] and by the limiting characteristics of the recording system.[9] The amount of this distortion can be estimated if the necessary information about sampling and recording systems is available.[10] In the rapid arterial dilution curve recorded after injection of dye into the left heart, any such distortion will be proportionally greater. For these reasons we have described our technique in some detail.

METHODS

The studies were made during diagnostic catheterization of the left and right sides of the heart. Patients were fasting and premedicated with sodium pentobarbital, 100 mg., and morphine sulfate, 10 mg.

Injections of indocyanine green* were made into the left ventricle (LV), left atrium (LA), or main pulmonary artery (MPA), and arterial dilution curves were recorded with a Model 103 cuvette densitometer† and either a direct-writing Poly-Viso‡ or DR-8 recorder.§ The response of either combined densitometer-recorder system to a square-wave change in optical density was such that 90 per cent of full response occurred in 0.04 second.

Routine catheterization of the right heart was performed; MPA injections were made with the catheter tip placed just distal to the pulmonic valve. LA injections were made through a polyethylene catheter (I.D. of 0.58 mm.) introduced after transbronchial[11] or percutaneous dorsal[12] needle puncture. LV injections were made through this catheter advanced from the LA, or through a 20-gauge needle inserted directly into the ventricle through the anterior chest wall.[13]

Except in those patients in whom the left ventricle was punctured directly, a period of rest in the supine position was allowed after the introduction of catheters and removal of needles and bronchoscope, before recording the dilution curves. When more than one curve was recorded, the interval between the two was as short as possible, varying between 3 and 5 minutes.

The dye was injected from syringes adjusted to deliver constant volumes. Two milliliters of a 3-mg./ml. solution were given into the MPA catheter, and 0.5 ml. of a 9-mg./ml. solution, into the left-heart catheter. Catheters were saline-filled, and were not flushed after the injection. The measured duration of injection was always less than 1 second. The exact amount of dye delivered was measured later by reproducing the injection in vitro, collecting the efflux from the catheter tip, and measuring its content of dye after volumetric dilution. Fifteen pairs of duplicate measurements by this technique had a coefficient of variation of 2.04 per cent.

Blood was sampled from the right brachial or femoral artery through a No. 18 Riley needle connected to the cuvette densitometer by 15 cm. of polyethylene tubing (I.D. of 1.14 mm.). The volume of the sampling system from needle point in the artery to the midpoint of the cuvette was 0.35 ml. The rate of blood flow was 0.6 ml./sec., maintained by a motor-driven syringe. Earlier studies in this laboratory[10] have shown that the effects of this sampling method on the dye-concentration curve occurring in the artery are: a prolongation of appearance time by 0.7 sec., build-up time by 0.5 sec., mean transit time by 0.7 sec., and slope time by less than 1 per cent, and a reduction of peak concentration by 7 per cent. For the purpose of this study, we did not consider it necessary to correct our data for these effects.

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*Cardiogreen: Hynson, Westcott and Dunning, Inc., Baltimore, Md.
†Colson Corporation, Elyria, Ohio.
‡Sanborn Company, Waltham, Mass.
§Electronics for Medicine, White Plains, N. Y.

Each curve was calibrated by the integrated sample method.[14] When two or more curves were recorded in one patient, the separate calibration factors were averaged, and that figure was used for all calculations. Replicate determinations of calibration factor in 31 patients (73 curves) had a coefficient of variation of 2.48 per cent.

Appearance time and build-up time were measured directly from the curve; peak concentration was expressed as the peak concentration (milligrams per liter in plasma) divided by the dye dose (milligrams per kilogram of body weight). After replotting semilogarithmically, the slope time was measured as the time taken for the extrapolated downslope to descend one log cycle, i.e., the time required for a 90 per cent decrement in concentration. Cardiac output was calculated in the usual way.[15]

CLASSIFICATION OF PATIENTS

Of 33 consecutive patients in whom catheterization of the left heart was performed, 1 was excluded from the present report because of a left-to-right shunt, 1 because of uncertainty in the final diagnosis, and 2 because of technically unsatisfactory dye studies. The remaining 29 patients ranged in age from 8 to 63 years; 14 had disease of the mitral valve alone, 10 of the aortic valve alone, 4 of both valves, and 1 had no valvular disease. In these patients, 25 curves were recorded after LA injection, 8 after LV injection, and 22 after MPA injection.

The regurgitation at each valve was graded separately, using all available diagnostic information. In the 12 patients with mitral valvular disease who were treated surgically, emphasis was placed on the operative findings. The degree of valvular stenosis has been disregarded in this assessment.

The criteria used in grading mitral regurgitation were: *Grade 0*—no mitral systolic murmur and no regurgitation detected at operation; *Grade 1*—mitral systolic murmur of Grade 1 or 2 intensity, radiologic LA enlargement at least 1+, and slight regurgitation palpable at operation; *Grade 2*—mitral systolic murmur Grade 3 or louder, LA enlargement 2+ or more, and moderate regurgitation palpable at operation; *Grade 3*—gross left heart enlargement, left ventricular hypertrophy by electrocardiogram and free regurgitation at operation.

For aortic valvular disease, the criteria for regurgitation were: *Grade 0*—no aortic diastolic murmur on repeated examinations; *Grade 1*—aortic diastolic murmur present, but arterial diastolic pressure above 70 mm. Hg (measured by arterial puncture at cardiac catheterization); *Grade 2*—murmur present, pulse pressure greater than 70 mm. Hg, and diastolic pressure above 40 mm.; *Grade 3*—pulse pressure greater than 100 mm., diastolic pressure below 40 mm., and gross left ventricular dilatation.

RESULTS* AND DISCUSSION

Measurement of Cardiac Output.—The validity of the indicator-dilution method for measuring cardiac output has been firmly established on theoretical grounds, and by model and clinical investigations.[16] In 8 patients the reproducibility of our measurement of output was tested by making two injections of dye *into the same site* less than 5 minutes apart (Fig. 1,*A*). The mean of outputs calculated from the first injection was 6.21 L./min., and from the second injection it was 6.20 L./min., with no systematic difference between the two; the average difference between two measurements in one individual was 0.36 L./min. (S.D., 0.17 L./min.).

In contrast, when two injections less than 5 minutes apart were made successively *into different sites* (the LA and MPA) in 15 patients (Fig. 1,*B*), a significant systematic difference between the two measurements of output was

*Copies of a table containing the measurements made from each of the 55 dilution curves reported in this study and other pertinent data may be obtained upon request to the authors.

found ($p < .01$). The output calculated from LA injections (mean, 5.59 L./min.) was, on the average, 0.39 L./min. higher than that calculated from MPA injections (mean, 5.20 L./min.). The order in which the injections were made did not apparently affect the result. A probable explanation, discussed by Dow,[16] is that extrapolation of the downslope on replotted curves may exclude recirculated dye more completely when the injection and sampling sites are close together. This explanation is supported by our finding a significantly longer interval ($p < .001$) between appearance time and the first evidence of recirculation (departure from the exponential downslope) for MPA injections (mean, 15.1 sec.; S.D., 3.3 sec.) than for LA injections (mean, 10.5 sec.; S.D., 2.8 sec.). Although not conclusive, this suggests that some recirculation is included in the estimated area of the primary curve with MPA injections, giving a falsely low estimate of the cardiac output.

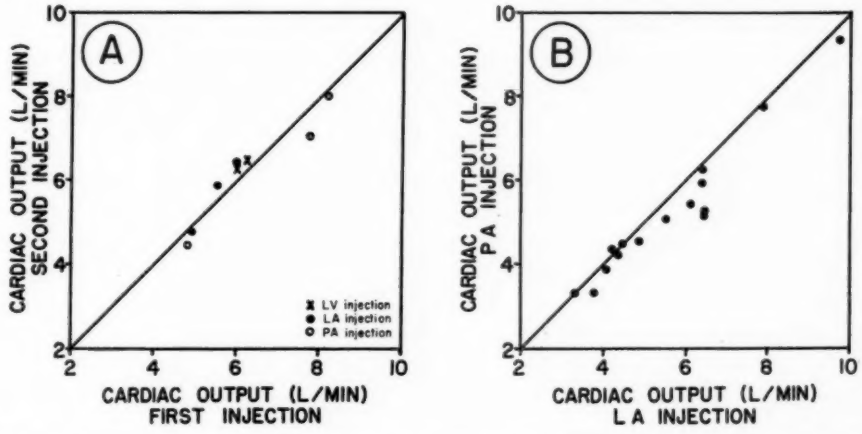

Fig. 1.—Comparison between the values for cardiac output measured by two rapidly consecutive injections of dye: *A*, into the same site, in 8 patients; *B*, into left atrium and pulmonary artery, in 15 patients. There is no significant difference between outputs calculated from successive injections into the same site. The output calculated from injection into the left atrium is slightly but significantly higher than that calculated from injection into the pulmonary artery (mean difference, 0.39 L./min.; $p < .01$).

Estimation of Valvular Regurgitation.—The evaluation of any test for regurgitation requires a selection of trial patients in whom the severity of regurgitation is established by independent criteria. There is at present no entirely reliable method, with the possible exception of cineangiocardiography, for measuring valvular regurgitation in man. The best evidence available to us was that provided by surgical exploration, and this is only crudely quantitative. The apparent accuracy of a test may be influenced in either direction by this limitation.

Any concentration or time component of a dilution curve is affected not only by regurgitation, but by the flow and volume of blood within the segment of the circulation examined,[1,4] and by other factors.[3] To estimate regurgitation clinically, a correction must be devised for the other variables. Discrimination between the effects of regurgitation and those of a large volume is the most difficult problem, perhaps because the effects are produced in the same way.

It is of theoretical interest that in our data the appearance time was not different in the presence of valvular regurgitation (Fig. 2). Korner and Shillingford found, in their circulatory model, that the introduction of a regurgitant "mitral" valve, without change in flow or volume, caused a shortening of the appearance time, and they reasoned that the same change was evident in curves recorded from patients with valvular regurgitation.[1,2] In our results, the presence of significant valvular regurgitation did not apparently influence the inverse relationship existing between appearance time and cardiac index (Fig. 2). Any reasoning based on the assumption that a significant reduction in appearance time occurs in man as a result of regurgitation[3,6,17] should be regarded, therefore, with some caution.

When a simple ratio of curve components to be used as an index for regurgitation is selected, the choice need not be entirely empirical. In Fig. 3, it is clear that the peak concentration (expressed as milligrams per liter per milligrams per kilogram) was relatively insensitive to flow but reduced by regurgitation, whereas the slope time was inversely related to flow and prolonged by regurgitation, at least when the cardiac index was low. Therefore, the ratio of peak concentration to slope time may be greatly reduced by regurgitation, although relatively less affected by changes in flow. A large volume would be expected to produce an effect qualitatively similar to that of regurgitation.

The values of the ratio of peak concentration to slope time calculated from injections of dye into the left heart are shown in Fig. 4, related to the grade of regurgitation. As can be seen, a good separation between the four grades is obtained in all three groups, better in mitral than in aortic regurgitation. Although overlap between groups is to be expected, an arbitrary value of 35 for LA in-

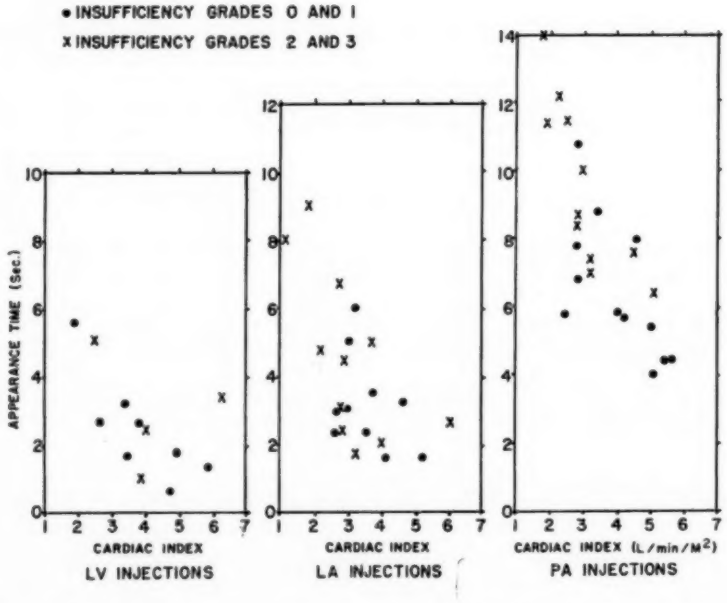

Fig. 2.—The relationship between cardiac index and the appearance time of dye at the systemic artery after injection into the left ventricle, left atrium, and pulmonary artery. The relation is not influenced apparently by the presence of valvular regurgitation.

jections divides significant (Grades 2 and 3) from insignificant (Grades 0 and 1) mitral regurgitation, with only one false positive result, and divides aortic regurgitation similarly, with only one false positive and one false negative result. This finding, in the presence of a wide range of cardiac outputs (1.17 to 8.90 L./min.), suggests that the ratio of peak concentration to slope time is somewhat independent of flow. An unusual volume of blood between injection and sampling sites, however, probably produced the low value of the ratio in one patient (designated by the arrow in Fig. 4,*C*) who had a large aortic aneurysm but no valvular regurgitation.

Ratios between other components of dilution curves have been used as indices of regurgitation, but when applied to our data, none gave as good results as did the ratio of peak concentration to slope time. In particular, the ratios of appearance time to "spread,"[6] of slope time to build-up time and of disappearance time to build-up time,[4] of "forward triangle" to total area,[4] and of disappearance time to appearance time,[17] all gave more false results than did the ratio of peak concentration to slope time. The ratio of least concentration to recirculation peak[18] is not available from our curves, because we discontinue the record before the recirculation peak in order to minimize the amount of blood withdrawn, and to maintain a relatively high concentration of dye in the calibrating sample.

It was anticipated that dilution curves recorded after injection of dye into the left heart would be more sensitive to mitral and aortic regurgitation than those recorded after MPA injection, the variable volume of blood in the lungs having been excluded. In Fig. 5, however, which shows the values of the ratio of peak concentration to slope time from the MPA injections in 22 of the 29 patients in this study, the separation between significant and insignificant regurgitation is essentially the same as that obtained by injections into the left heart (Fig. 4). Moreover, no wrong diagnosis of regurgitation made from a MPA injection was corrected by the result of the injection into the left heart in that patient.

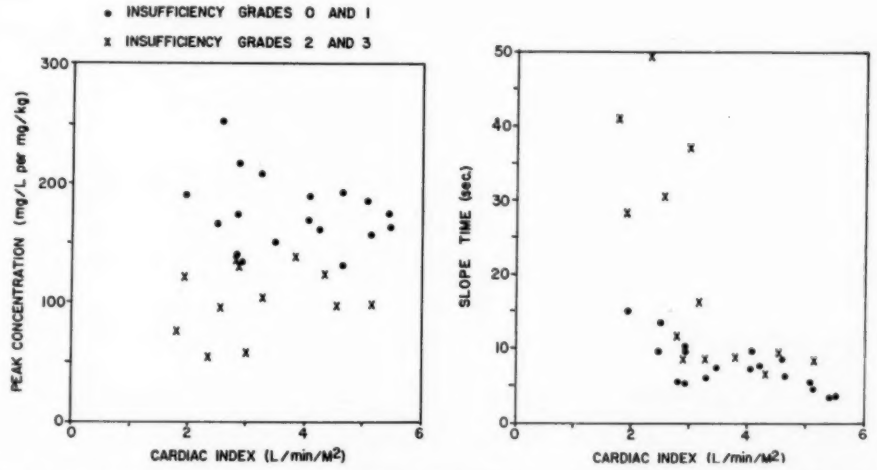

Fig. 3.—The relationships between cardiac index and peak concentration, and between cardiac index and slope time, for injections into the pulmonary artery. (These figures include data obtained in 22 of the patients described in the text, and in 9 others who did not undergo catheterization of the left heart.)

Detection of Left-to-Right Shunts.—In addition to providing a measurement of cardiac output and an assessment of valvular regurgitation, arterial dilution curves recorded after injections of dye into the left heart reveal also the presence of left-to-right shunts by the appearance of early recirculation on the downslope.[19]

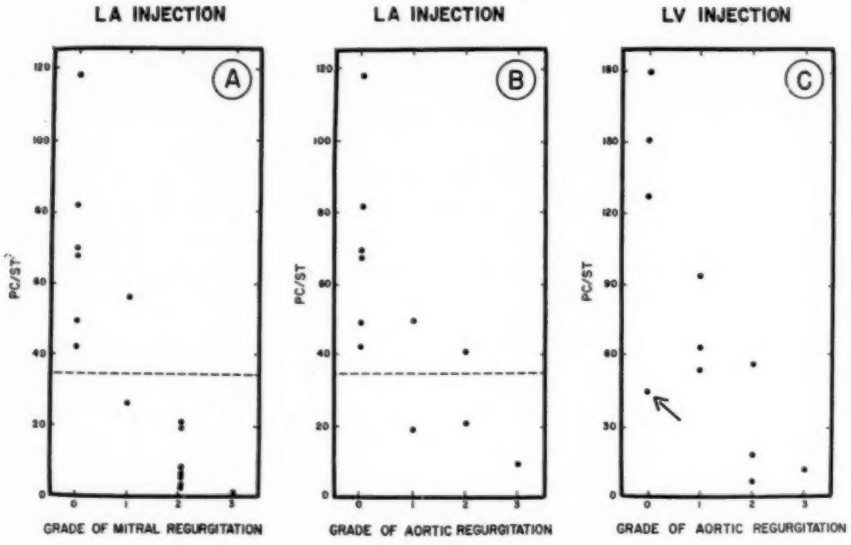

Fig. 4.—The ratio of peak concentration to slope time in curves obtained after injections into the left heart, related to the severity of regurgitation. Patients with mitral regurgitation and no aortic regurgitation are shown in *A*; patients with aortic regurgitation but no mitral regurgitation are shown in *B* or *C*, depending on the site of injection. Of the 6 patients with no regurgitation shown in both *A* and *B*, 4 had pure mitral stenosis, 1 had aortic stenosis, and 1 had no valvular disease.

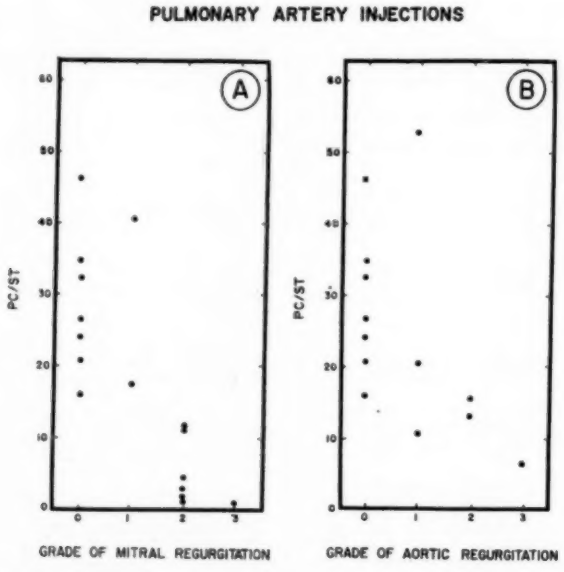

Fig. 5.—The ratio of peak concentration to slope time in arterial dilution curves recorded after injections into the pulmonary artery, related to the severity of regurgitation. *A*, Patients with mitral but no aortic regurgitation. *B*, Patients with aortic but no mitral regurgitation. Patients with no valvular regurgitation form the control group in both *A* and *B*.

Although patients with shunts have been excluded from this study, previously unsuspected small shunts have been detected in this laboratory on two occasions in patients with mitral valvular disease.

CONCLUSIONS

1. Arterial dilution curves recorded after the injection of dye into the left heart give a valid measurement of cardiac output. The figure so obtained is significantly higher than that obtained by injections into the pulmonary artery, by a small amount (mean difference, 0.39 L./min.; $p < .01$).

2. The ratio of peak concentration to slope time in such dilution curves recorded from the left heart gives a readily calculated index of the presence and severity of valvular regurgitation. The incidence of false diagnosis using this ratio was approximately the same for injections made into the left heart as for those made into the pulmonary artery.

We acknowledge gratefully the cooperation of Dr. Henry Bahnson and Dr. Frank Spencer, who performed the catheterizations of the left heart, and the technical assistance of Miss Mary Lou Sparger.

ADDENDUM

Additional patients have been studied since this article was submitted for publication, and a total of 50 patients has now been studied by injection of dye into the left atrium. When a peak concentration to slope time ratio of less than 23 is used as an indication of significant mitral regurgitation, the incidence of false tests is 4 per cent (1 false positive in 27 control subjects, and 1 false negative in 23 cases).

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Diastolic Movements of the Precordium in Mitral Stenosis and Regurgitation*

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The rate of filling of the left ventricle should be, in part, directly related to the size of the mitral opening. Physiologic methods presently in use have measured the rate of emptying of the left atrium, either by direct recordings from the left atrium or from the reflected wave sensed by wedge catheter.[1-7]

We have studied this same event but from a different approach; we have recorded the movement of the chest wall, overlying the left ventricle, with special attention to the movement in diastole—the period of filling of the left ventricle. The fact that this measurement can be made quickly, easily, and repeatedly makes this approach attractive. The tracing obtained is designated the *apex-cardiogram* (ACG).

MATERIAL AND METHOD

The equipment used for recording the phonocardiograms was the Sanborn Twin-Beam phonocardiograph with a Sanborn microphone (62-1500-C-13). The phonocardiogram (PCG) at all four classic auscultatory areas was obtained, with the carotid tracing, jugular venous tracing, and electrocardiogram as reference tracings. The paper speed was 75 mm. per second. These reference tracings and the ACG were recorded by means of a pulse crystal microphone (Sanborn No. 374) which reproduces an electrical signal proportional to change in pressure in the tubing. Frequency response of this crystal microphone is from 1 to 1,000 cycles per second. A descriptive detailed study of the electronic characteristics of this system has been described by Miller and White.[8]

After completion of the routine recording of the PCG, the point of maximal impulse in the left lateral decubitus position was determined by examination, and a left ventricular complex was confirmed on the electrocardiogram from this point (qR complex). The sound microphone was then positioned so that the pickup bell with side opening tube was placed directly over the point of maximal impulse, and the ACG was recorded simultaneously with the phonocardiogram.

This series of 87 patients was selected from over 200 patients with mitral valvular disease.

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Supported in part by a Graduate Training Grant in Cardiology from The National Heart Institute and by funds from the Kansas Heart Association.

Received for publication Dec. 17, 1959.

*Requests for reprints should be addressed to: Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, La Jolla, California.

Selection was based only on the availability of diagnostic proof; all cases chosen were documented by cardiac catheterization, operation, or necropsy. No case in which this information was available was excluded from the study.

Selection of patient material for this study was based entirely on the availability of documentation of the physiologic lesion. The 40 normal subjects were chosen on the basis of normal physical examination. In 36 patients, mitral stenosis was confirmed by operation and occasionally at necropsy. In 12 patients, predominant mitral stenosis and a lesser degree of mitral regurgitation were confirmed by operation. Of the 39 patients with mitral regurgitation as the sole or principal lesion, 7 cases were confirmed by operation, 12 at necropsy, 8 by cardiac catheterization, and the other 11 were identified on the basis of acceptable clinical data: blowing, regurgitant systolic murmur, lessened mitral first sound, palpable left ventricular lift, left ventricular hypertrophy by electrocardiogram, etc. In no case was the selection of the patient based on the adequacy of the apexcardiogram.

In this fashion the following groups of patients were selected for further study. *Group I:* 36 patients with pure mitral stenosis (MS); *Group II:* 12 patients with mitral stenosis and mitral regurgitation but with dominant stenosis (MSmr); *Group III:* 26 patients with pure mitral regurgitation (MR); *Group IV:* 13 patients with mitral regurgitation and mitral stenosis but with dominant regurgitation (MRms); *Group V:* 40 normal subjects.

The material was separated into the afore-mentioned groups, and the grouping was done on the basis of clinical findings, largely on the presence or absence of a mitral regurgitant jet at operation.

Analysis of the ACG was made in each case, with special attention being given to the diastolic filling wave which begins at the base of the ACG and ends with the beginning of the following systolic wave. When the filling wave rose sharply from its origin to a definite peak and then continued to its termination at the beginning of the following systolic wave, the initial early filling component was designated as the "rapid filling wave" (RFW), and the delayed component was designated as the "slow filling wave" (SFW) (Fig. 1). The angles that the RFW and the SFW made with the base line or horizontal were designated as the "rapid filling angle" (R) and "slow filling angle" (S), respectively. The total angle (T) was determined by drawing a line from the base of the ACG to the summit of the following systolic wave and measuring the angle between this line and the base line (Fig. 1). In order to compare those apexcardiograms which had different amplitudes, the ratio of the T angles to the filling angles was calculated, i.e., T/R and T/S.

An examination was also made of the ACG with special attention to the shape of the systolic wave, duration and amplitude of RFW, duration of the SFW, and the presence of an "a" wave (atrial wave). Left ventricular systole and diastole were measured by means of a previously described technique.[9]

The size of the mitral valve was estimated by the surgeon at the time of operation. However, in 12 cases the size of the mitral valve was determined by means of Gorlin's formula[11,12] with data obtained during cardiac catheterization. Right ventricular and left atrial pressures were obtained by the surgeon in most of these cases before and after valvulotomy.

The results were analyzed statistically and the "t" test was used to determine significance between the groups.[13]

All reported angles and intervals represent the mean values of measurements made in five consecutive cardiac cycles. Vertical lines in the tracings are 0.04 second apart. The following abbreviations have been employed throughout this study: *1*, First sound. *2*, Second sound. *3*, Third sound. *4*, Fourth sound. *SM*, Systolic murmur. *DM*, Diastolic murmur. *ASM*, Atrial systolic murmur. A_2, Aortic valve closure. P_2, Pulmonic valve closure. *OS*, Opening snap. *R*, Rapid filling angle. *S*, Slow filling angle. *T*, Total angle. *RFW*, Rapid filling wave. *SFW*, Slow filling wave. *T/R*, Total angle rapid filling angle ratio. *T/S*, Total angle slow filling angle ratio.

RESULTS

Group I: 36 Patients With Pure Mitral Stenosis (MS).—One of the most striking findings in this group was the absence of RFW. The study of the diastolic filling period revealed a SFW with no evidence of rapid filling. A rapid filling

angle could not be determined (Fig. 2). The slow filling angle ranged from 10° to 52°, with a mean value of 23° (23° ± 9.7°). In only 3 of the 36 cases was the S angle above 35° (40°, 48°, 52°). The T angle ranged from 20° to 80°, with a mean value of 40° (40° ± 12.6°). The T/S ratio, except in 3 cases (0.72, 0.84, and 0.89) ranged from 1 to 3.3, with an average of 1.7 (1.7 ± 0.60) (Table I). The frequency distribution of this group is shown in Fig. 3.

When compared to that of a normal control group of 40 cases, the "t" test in this group for S angle, T angle, and T/S ratio showed $p < .001$ for the S angle and T/S ratio. T angle was not statistically significant.

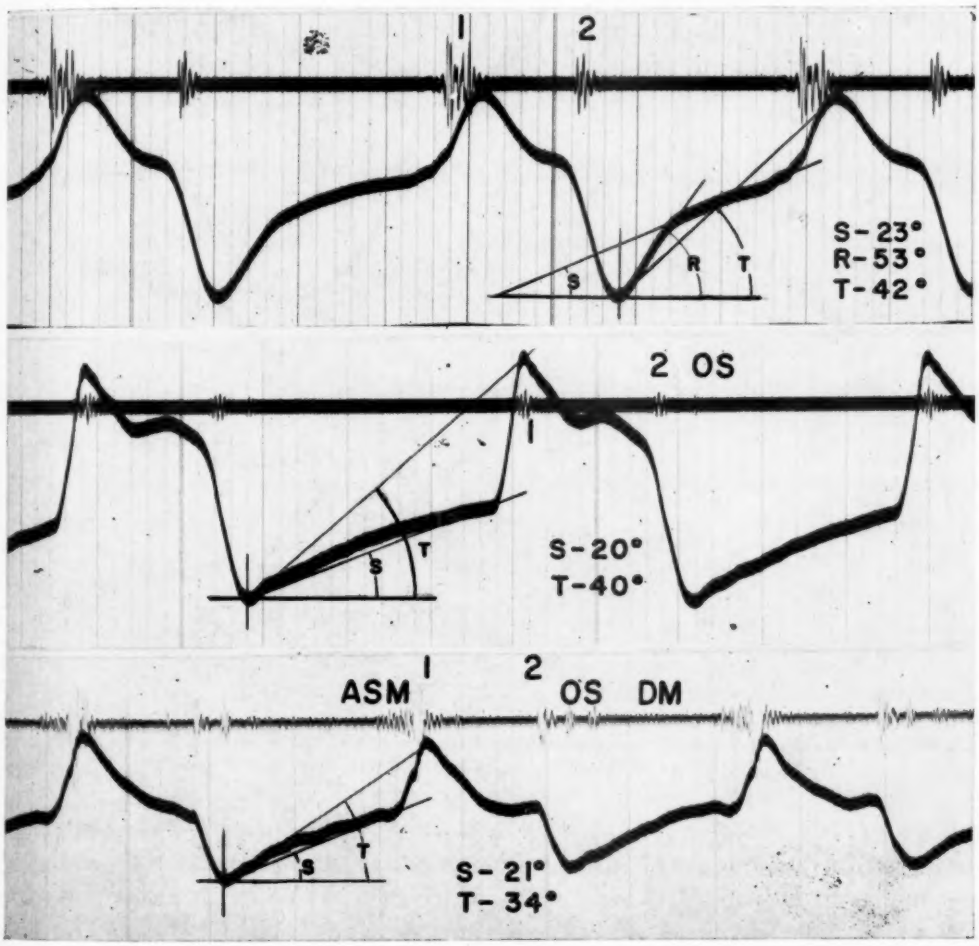

Fig. 1.—*A*, Normal subject. ACG demonstrating the derivation of the R, S, and T angles. *B* and *C*, Mitral stenosis. RFW replaced by SFW. OS coincident with the beginning of the filling wave.

The Ry/V ratio was determined in 19 patients of this group from the left atrial or pulmonary wedge tracing, according to the criteria of Owen and Wood.[1] All 19 patients were found to have an Ry/V ratio of less than 1.5, as well as ACG findings without RFW, and S angles ranging from 16° to 32°. At operation, mitral stenosis without regurgitation was demonstrated in all 19 cases (Fig. 4).

Left ventricular systole ($M_1 - A_2$) in 24 cases varied from 0.24 to 0.32 second, with an average of 0.28 second. Left ventricular diastole in 23 patients ranged from 0.34 to 0.53 second.

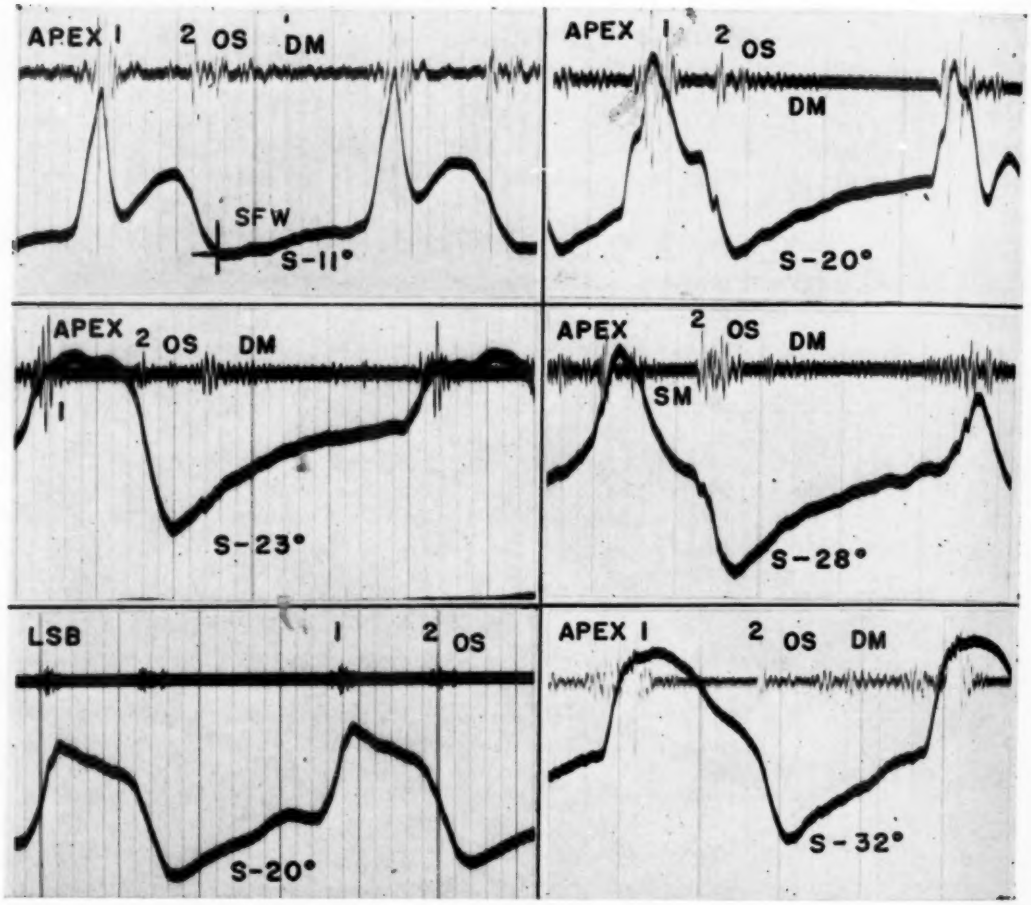

Fig. 2.—Pure mitral stenosis. Eight cases demonstrating absence of RFW with slow left ventricular filling. Amplitude of the tracing is essentially the same in all cases.

Group II: 12 Patients With Mitral Stenosis and Regurgitation With Dominant Stenosis (MSmr).—The ACG findings in this group were essentially the same as those in Group I. The ACG revealed absence of a RFW in all cases (Fig. 5). The S angle ranged from 16° to 38°, with an average of 24° (24° ± 6°). The T/S ratio ranged from 1.2 to 1.8, averaged 1.5 (1.5 ± 0.21). The T angle ranged from 29° to 54°, with a mean value of 37° (37° ± 9.5°) (Fig. 3 and Table I). Again the filling angle and T/S ratio were statistically significant when compared with the control group ($p < .001$). The difference in the p values between this group and the group with pure MS was not significant for the S angle and T/S ratio ($p = .80$ and $p = .30$, respectively).

Group III: 26 Patients With Pure Mitral Regurgitation (MR).—The ACG revealed a RFW with a duration of from 0.06 to 0.14 second (mean, 0.08 second).

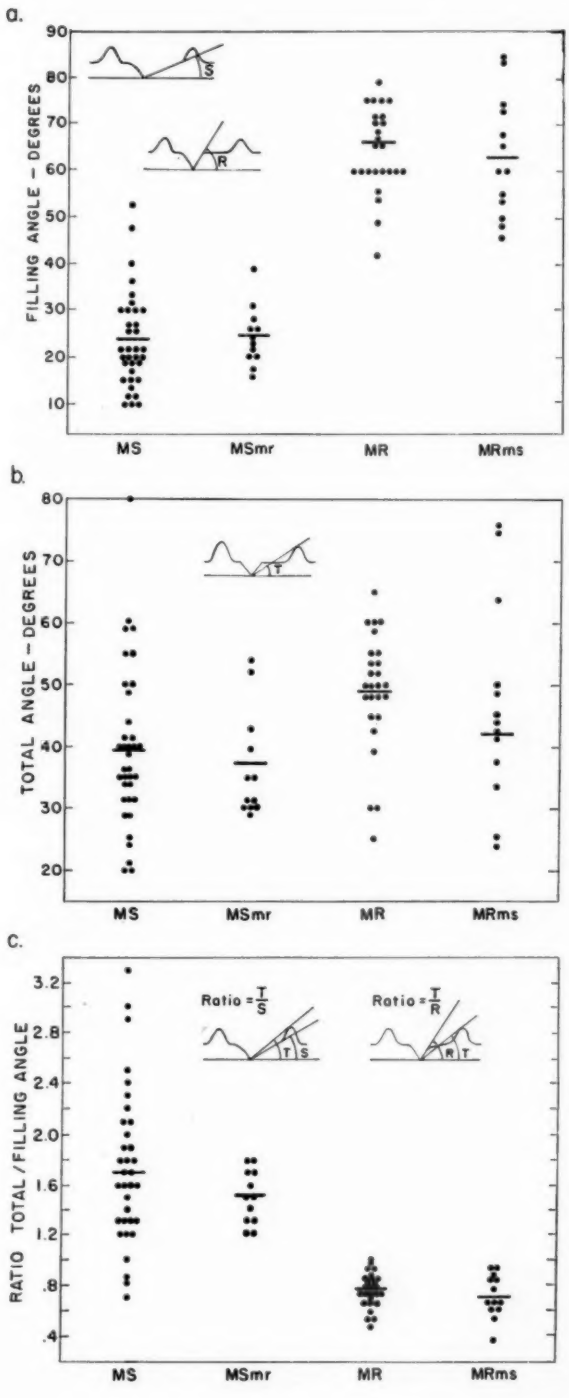

Fig. 3.—Frequency distribution of filling angles and ratios in patients with mitral valvular disease. Note the small filling angle in the groups with MS and MSmr, and the large angle in the groups with MR and MRms. Note a T/S ratio above 1 in the majority of the patients with pure or dominant MS and below 1 in patients with pure or dominant MR. Observe in *c* that the T angle is essentially the same in all four groups, revealing that the amplitudes of the tracings were essentially the same.

The R angle ranged from 42° to 78°, with an average of 64° (64° ± 8.6°) (Figs. 3 and 9); the T angle ranged from 25° to 65°, with an average value of 49° (49° ± 10.4°). The T/R ratio ranged from 0.49 to 0.98, with an average of 0.76 (0.76 ± 0.13) (Table I). The height of the RFW was determined in relation to the total amplitude of the ACG, and varied from 12 to 50 per cent (average value, 31 per cent).

TABLE I. FILLING ANGLE AND RATIOS IN PATIENTS WITH MITRAL VALVULAR DISEASE

GROUP	R ANGLE (DEGREES)		S ANGLE (DEGREES)		T/R RATIO		T/S RATIO	
	RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
MS (36 patients)	—	—	10–52	23 ± 9.7	—	—	0.72–3.3	1.7 ± 0.60
MSmr (12 patients)	—	—	16–38	24 ± 6	—	—	1.2–1.8	—
MR (26 patients)	42–78	64 ± 8.6	—	—	0.49–0.98	0.76 ± 0.13	—	—
MRms (13 patients)	45–85	63 ± 13	—	—	0.39–0.90	0.71 ± 0.14	—	—
Control (40 patients)	32–77	54 ± 11.4	—	—	0.41–0.90	0.68 ± 0.13	—	—

The figure to the right of the ± sign is the standard deviation.

TABLE II. PRE- AND POSTOPERATIVE FILLING ANGLES AND RATIOS

MITRAL STENOSIS	R ANGLE (DEGREES)		S ANGLE (DEGREES)		T/R RATIO		T/S RATIO	
	RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Preoperatively	—	—	10–30	22 ± 5.9	—	—	1–3	1.8 ± 0.49
Postoperatively	31–75	53 ± 10.3	—	—	0.33–1.3	0.83 ± 0.23	—	—

The figure to the right of the ± sign is the standard deviation.

There was a statistically significant difference between the filling angle and ratios in this group and those of the group with mitral stenosis ($p<.001$). A comparison made between the filling angle in this group and that in a control group revealed a $p<.005$, and for the ratio, $p<.05$.

The Ry/V ratio in this group was above 1.8 in all patients.

Group IV: 13 Patients With Mitral Regurgitation and Mitral Stenosis With Dominant Regurgitation (MRms).—All patients in this group presented a rapid filling wave in the ACG as described for Group III. It was possible to differentiate

this group from the group with combined MSmr by the presence of a RFW (Fig. 10). All of the patients presented a systolic regurgitant and a mid-diastolic murmur at the apex. The R angle ranged from 45° to 85°, with an average of 63° (63° ± 13°). The T/R ratio was below 1 in all cases; it ranged from 0.39 to 0.90 and averaged 0.71 (0.71 ± 0.14) (Table I and Fig. 3). These values were

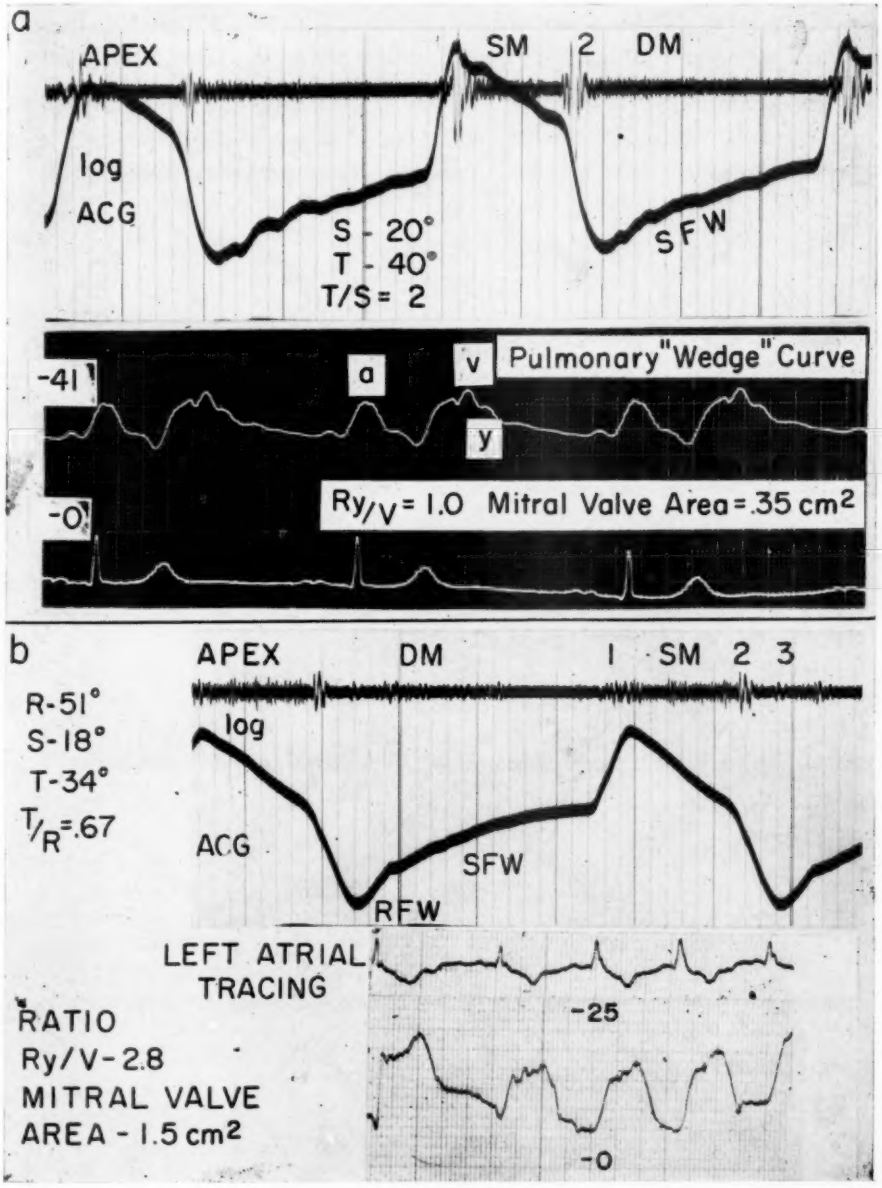

Fig. 4.—*a*, Mitral stenosis. Correlation of the filling wave in the ACG and the "y" descent of the V wave in the pulmonary wedge tracing. Note the slow "y" descent in the venous tracing and slow filling wave in the apexcardiogram. *b*, Mitral regurgitation. Correlation of the filling wave in the ACG and the "y" descent of the V wave in the left atrial tracing. Note the rapid "y" descent in the venous tracing and the presence of RFW in the ACG.

statistically not significant when compared with the group with MR, but were significant when compared with the group with MSmr, with $p<.001$ for the filling angle and ratio.

Mitral Stenosis: Pre- and Postoperative Findings.—The ACG was obtained before and after valvulotomy in 21 patients. Significant changes were noted in all tracings recorded after operation (Table II). The most striking finding was the appearance of a RFW after mitral valvulotomy in 19 cases (Fig. 6). In these postoperative recordings the R angle could then be determined, and ranged

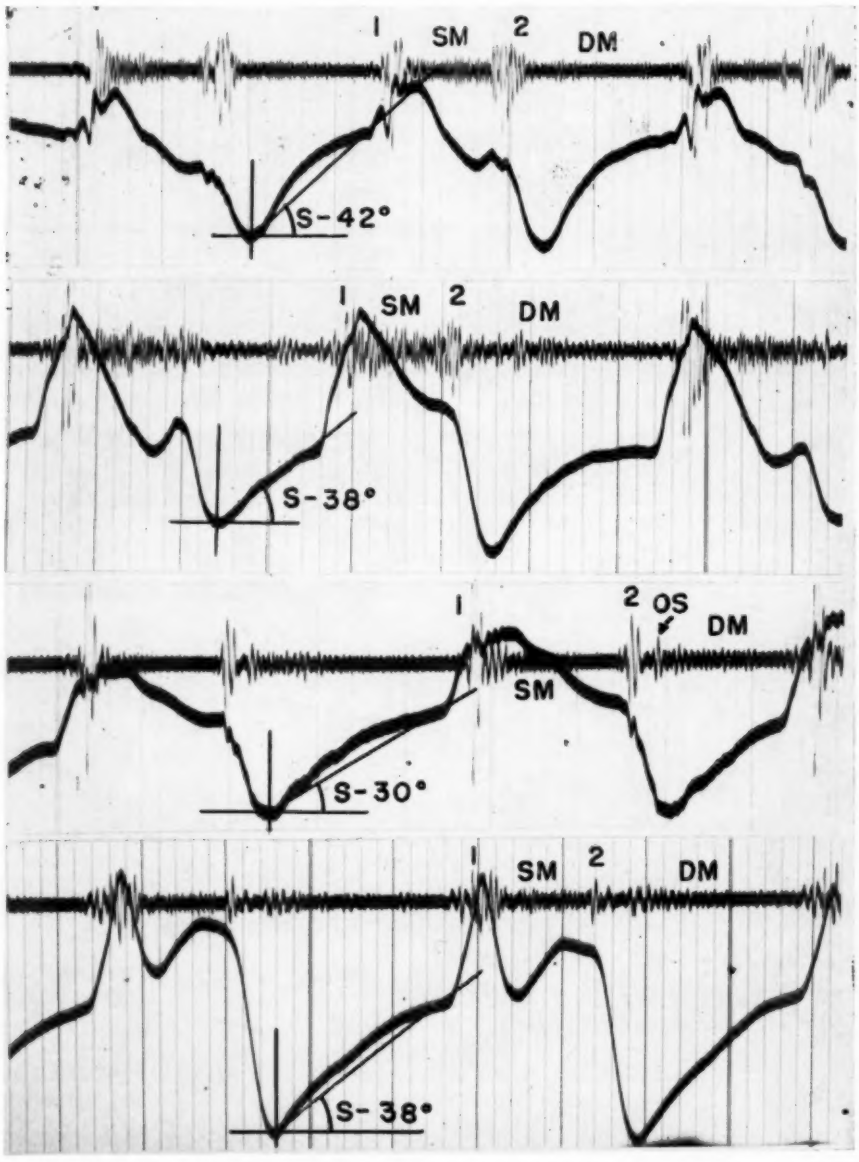

Fig. 5.—Combined mitral lesion with dominant stenosis. Four cases demonstrating absence of RFW. Note that the initial early component of the filling wave does not rise to a definite sharp peak. Compare with Figs. 6 and 10. Observe phonocardiographic signs of MS and MR.

from 31° to 75°, with a mean of 53° (53° ± 10.3°). The T angle ranged from 24° to 63°, with an average of 41° (41° ± 11.4°). The T/R ratio was 1 or below 1 in 19 cases, and ranged from 1.30 to 0.33 (0.83 ± 0.23). The presence of a RFW was confirmed by repeated ACG up to 1 year after mitral valvulotomy. In 19 cases the increase in the size of the mitral orifice after operation was also accompanied by a significant increase in the filling angle, as shown in Figs. 7 and 8, and a decrease in the T/S ratio. The T/S ratio was greater than 1 in the preoperative group and less than 1 in the postoperative group in the great majority of cases (Fig. 7).

A statistical analysis was made between the pre- and postoperative ACG findings. The difference between the filling angle and the ratio before and after valvulotomy revealed p=.001 for both measurements. The difference between the

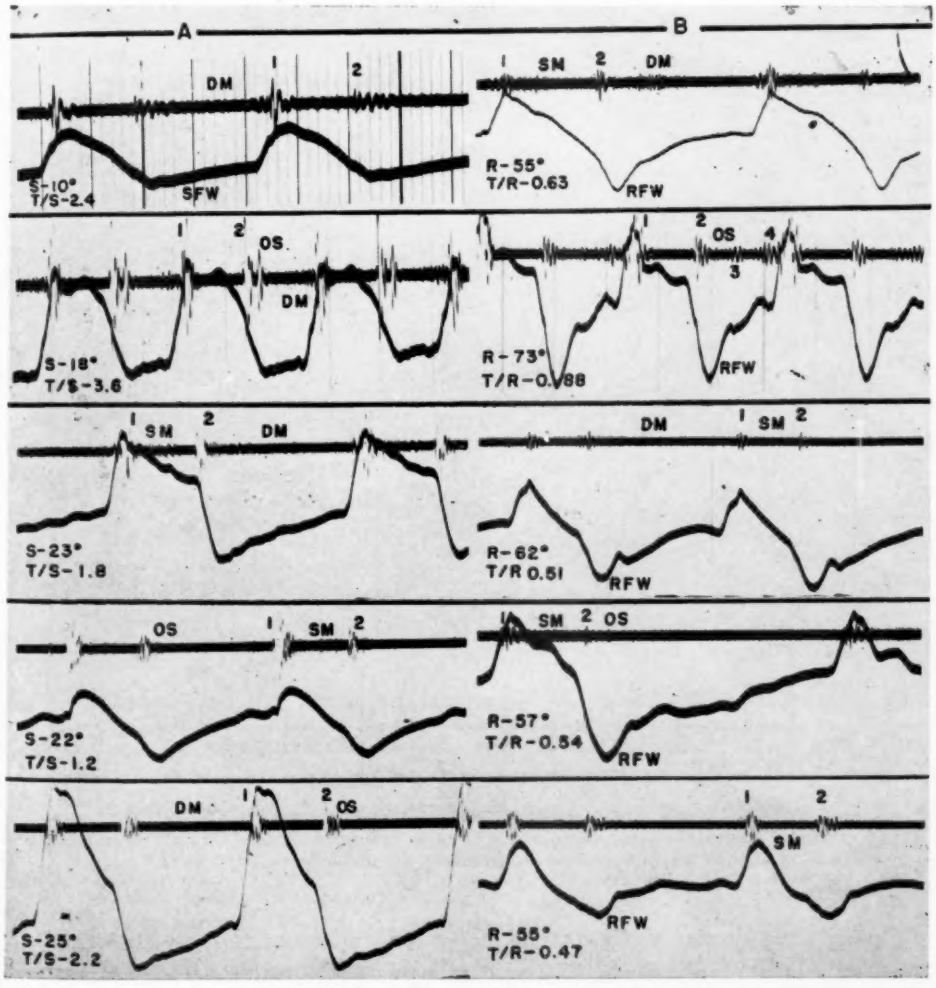

Fig. 6.—Mitral stenosis. *A*, Before mitral valvulotomy. Note absence of RFW in all cases. *B*, After valvulotomy. A definite RFW is recorded. Observe the acute angle of the RFW.

T angles before and after operation was not significant, since the amplitude of the tracings was maintained essentially the same.

Group V: Control Group of 40 Normal Subjects.—All cases in the control group had a RFW (Fig. 1), and the R angle varied from 32° to 77° (mean 54°; 54° ± 11.4°) The T/R ratio ranged from 0.41 to 0.90 (0.68 ± 0.13).

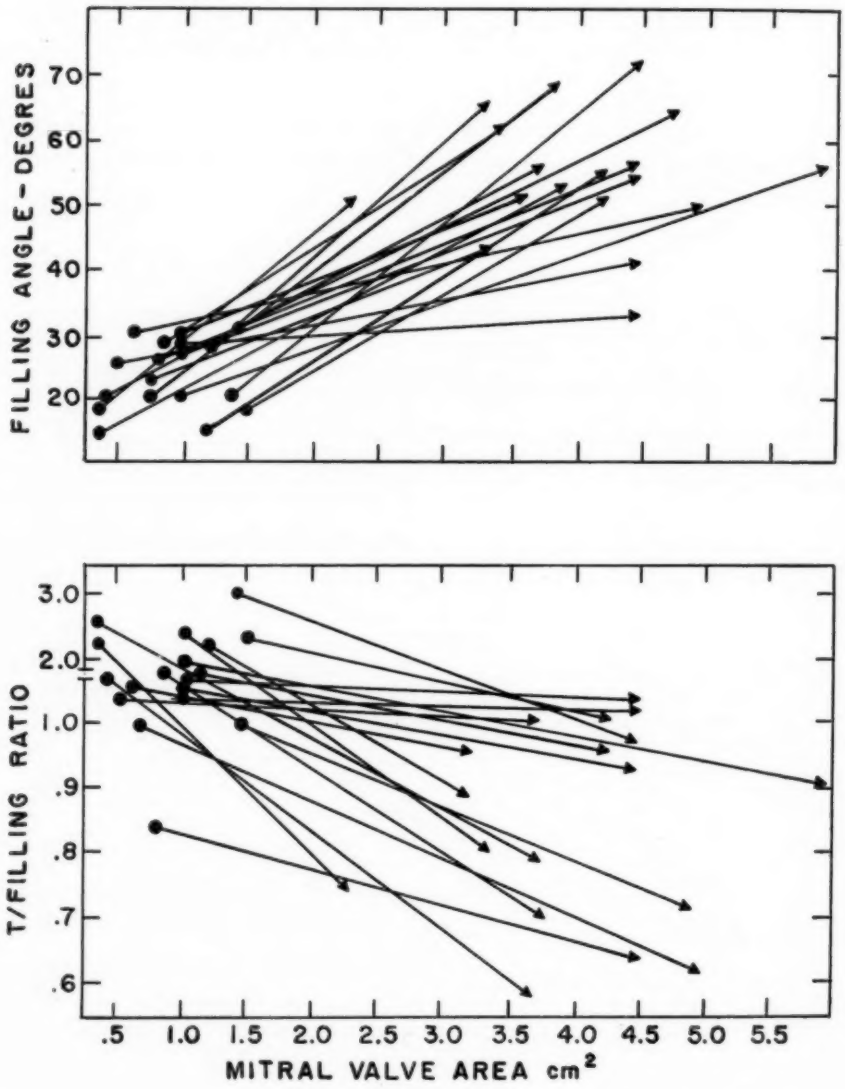

Fig. 7.—Mitral stenosis. Filling angle and T/S ratio before (•) and after mitral valvulotomy (→). Note increase in the filling angle and decrease in the T/S ratio after valvulotomy.

The control group could not be differentiated from the group with minimal to moderate mitral regurgitation on the basis of R angle and T/R ratio alone ($p = .005$ and $= .05$, respectively). However, patients with severe mitral regurgitation showed R angles larger than those of the control group.

DISCUSSION

As a means of discretely determining the presence of mitral obstruction in a patient with mitral valvular disease, this method seems to have as much value and reliability as the more complicated intracardiac approach. The same physiologic event is being analyzed: with the intracardiac formulas, one is interested in the rate of emptying of the left atrium, i.e., the descent of the V wave[1]; with this present technique we are studying the simultaneous event, the filling of the left ventricle, i.e., the rapid or slow filling wave (Fig. 4).

In common with the indirect methods currently employed (Ry/V,[1] 0.1 Ry/V,[14] and others[15-17]) this approach is limited to the detection of mitral stenosis, and is capable of doing so in the presence of mitral regurgitation. It will not yield quantitative information, i.e., valve size, nor will it differentiate a normal valve from most minimal mitral regurgitation.

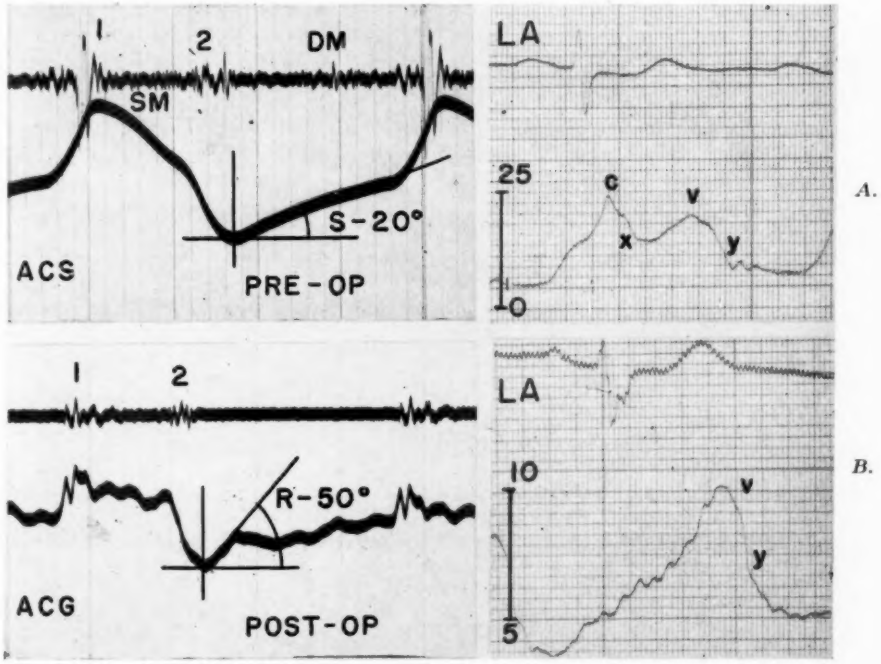

Fig. 8.—Mitral stenosis. *A*, Before mitral valvulotomy. Apexcardiogram without rapid filling wave. S angle of 20°. The left atrial curves show slow "y" descent of the V wave. *B*, One month after operation. Note presence of RFW with R angle of 50° and left atrial pressure curves with rapid "y" descent.

Statistical analysis ("t" test) reveals a high level of significance ($p<.001$) between normal subjects and patients with pure or dominant mitral stenosis. Likewise, statistically significant changes are seen in the ACG following mitral valvulotomy.

In the presence of combined mitral regurgitation and mitral stenosis the ACG seems to be of special value. In this circumstance (Figs. 5 and 10) the ACG continues to show absence of a RFW when stenosis predominates, and its presence when mitral regurgitation is the primary lesion.

Several investigators[18-24] have studied the apex impulse in relation to dilatation of ventricular chambers.

Eddleman and co-workers[25,26] have studied precordial movements, referring to their recordings as kinetocardiograms. Patterns referable to normal conditions and to valvular lesions have been described. The kinetocardiogram of Eddleman at the KV_4 position bears some relationship to the apexcardiogram in this report.

In patients with a significant degree of mitral stenosis there is an appreciable reduction in early left ventricular filling. The present study revealed the absence of a rapid filling wave in patients with a tight mitral stenosis (Fig. 2). Successful mitral valvulotomy should result in a significant increase in early left ventricular diastolic filling. In our series this has been true—with the replacement of the SFW by a more rapid filling phase after valvulotomy (Figs. 6-8). A change in functional grading from III-IV to I-II reflected considerable symptomatic improvement.

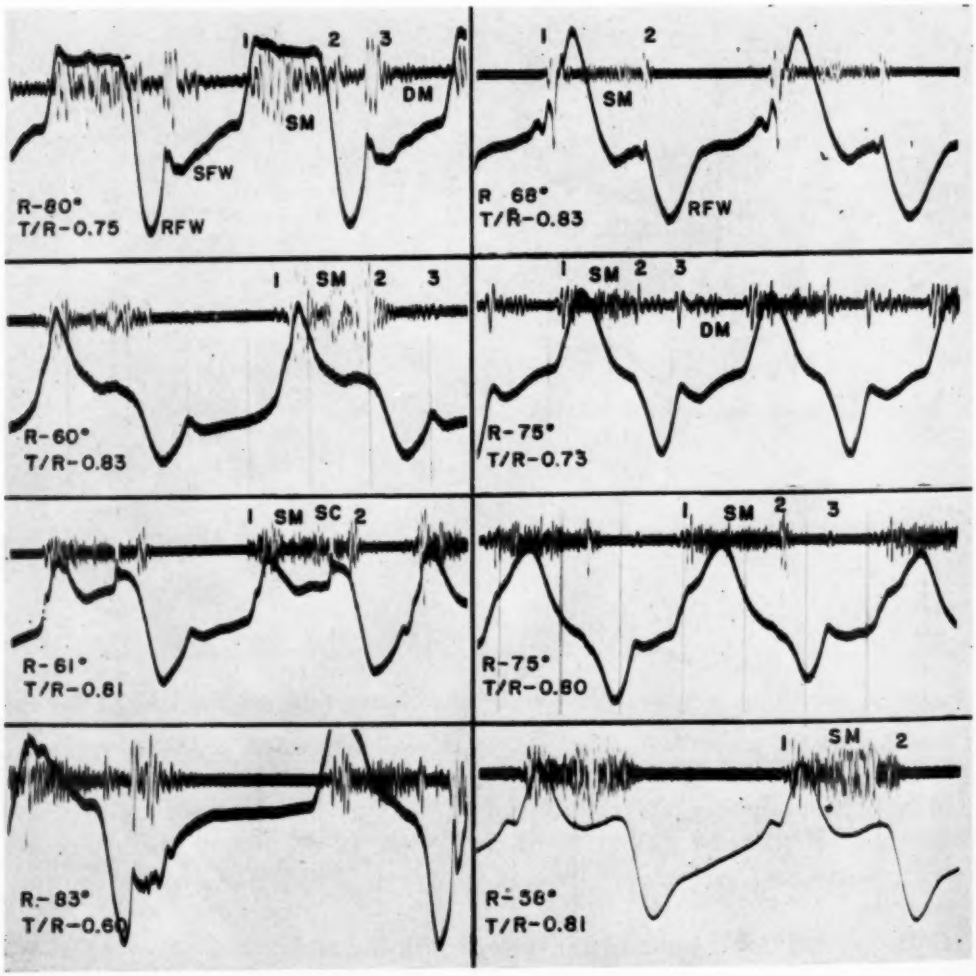

Fig. 9.—Pure mitral regurgitation. Eight patients demonstrating the presence of RFW. Note that the RFW rises sharply to a definite peak and then continues as slow filling wave. Compare with Figs. 5 and 10.

Occasionally in patients with severe mitral stenosis and marked pulmonary hypertension the right ventricle is so hypertrophied that it may form the anterior surface of the heart, with significant posterior displacement of the left ventricle. In such patients the apexcardiogram of the right ventricle may be easily detected[10] and the left ventricular ACG may not be recorded, which per se is of diagnostic importance. The precordial electrocardiogram revealing absence of left ventricular complex, which is characterized by a qR complex, helps identify the true nature of the apex beat. In our series of mitral stenosis the left ventricular ACG was not recorded in 5 cases.

In one patient a successful mitral valvuloplasty was performed on a regurgitant valve, with significant clinical improvement. The postoperative apexcardiogram showed replacement of the preoperative R angle of 60° by a slow filling wave with an S angle of 18° (Fig. 11, *A* and *B*). Six months after operation this patient deteriorated clinically and a loud systolic murmur was again heard at the

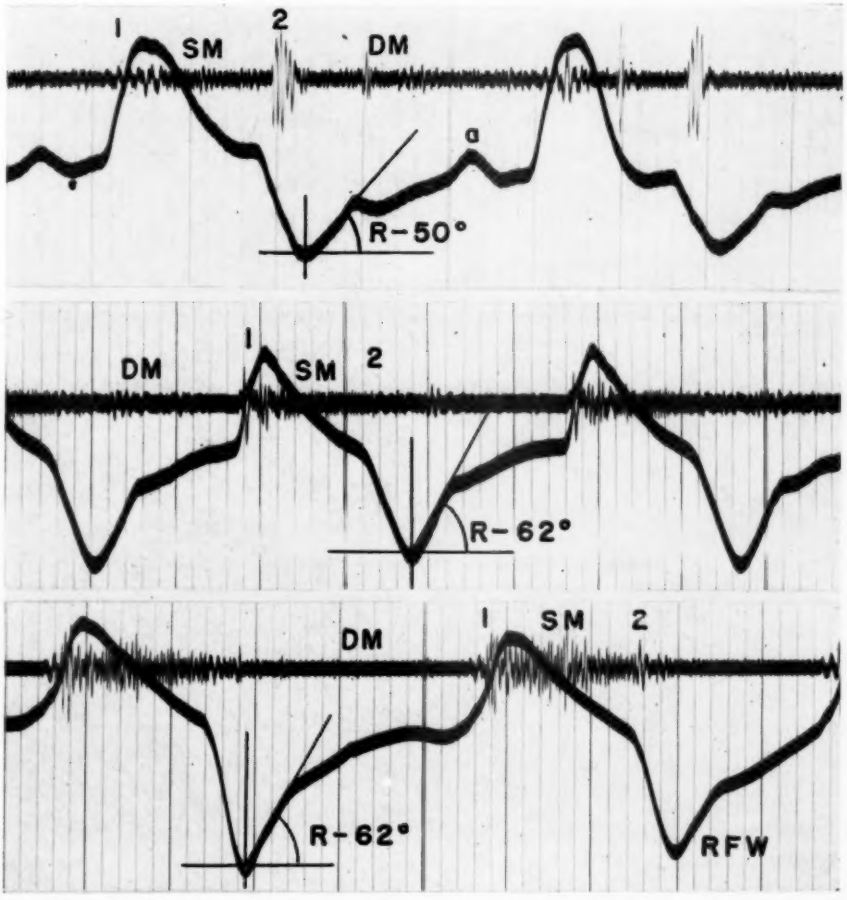

Fig. 10.—Combined mitral lesion with dominant mitral regurgitation. Apexcardiogram in 3 patients. Observe the presence of a rapid filling wave in all cases. The RFW is identified by its acute angle, with a definite transition to a slow filling wave. Amplitudes of the tracings are essentially the same. Systolic and diastolic murmurs at the apex. Compare with Figs. 5 and 9.

apex. The patient developed a significant degree of mitral regurgitation. The apexcardiogram revealed a reappearance of a RFW with an R angle of 64° (Fig. 11,*C*).

In patients with mitral regurgitation the duration of the rapid filling wave was short; it ranged from 0.06 to 0.14 second for a heart rate of 50 to 100 beats per minute. With a heart rate of 60 to 80 beats per minute the duration of rapid ventricular filling was nearly constant—from 0.08 to 0.10 second. It was noted that with increasing regurgitation the duration of early ventricular filling tended to shorten, indicating a diastolic flow at a high velocity.

In several instances we have found the ACG useful in confirming restenosis of the mitral valve after a successful valvulotomy. The ease of the method lends itself well to serial study.

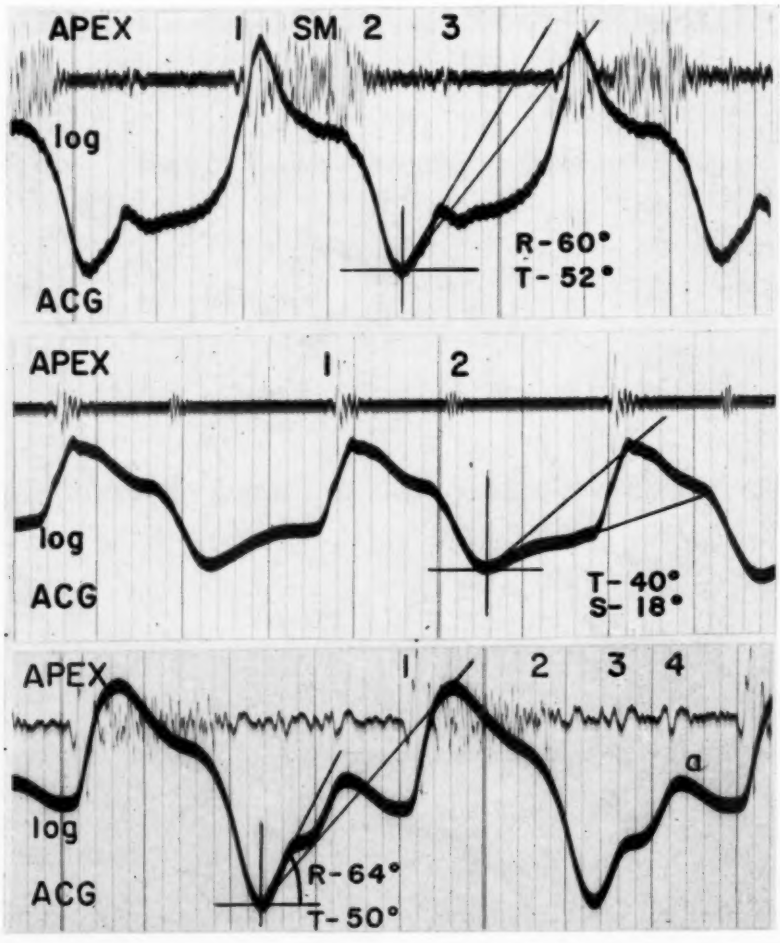

Fig. 11.—Pure mitral regurgitation. *A*, Before operation. Note RFW with R angle of 60°. High-amplitude systolic regurgitant murmur. *B*, One month after mitral valvuloplasty for correction of MR. Note disappearance of RFW with S angle of 18°. The systolic murmur particularly disappeared. *C*, Six months after operation. Note reappearance of RFW with an R angle of 64°, as was present before operation. High-amplitude regurgitant murmur is recorded with third and fourth sounds. Giant "a" waves in the ACG.

In a series of 18 patients, the apexcardiogram was analyzed and the presence or absence of relative stenosis suggested without prior recourse to the clinical and surgical findings. In this series, the presence or absence of significant stenosis was correctly identified in every case by means of the apexcardiogram alone.

The technique of recording the apexcardiogram is one which must be developed by practice, and initial attempts usually result in artefactual curves. However, in our last 50 patients an adequate apex tracing was recorded in 48 of them. This is certainly a more reproducible measurement than the "wedge" curve and, of course, much easier and quicker to make.

Within the limits described above, we feel that this method is a valuable adjunctive approach to diagnosis, useful when the presence or absence of significant mitral stenosis is in question. Because of simplicity and ease of performance, we feel it merits consideration in the evaluation of a patient with mitral valvular disease.

SUMMARY AND CONCLUSIONS

1. Eighty-seven patients with mitral valvular disease were studied. This group consisted of 36 patients with pure mitral stenosis, 12 patients with dominant mitral stenosis and minimal mitral regurgitation, 26 patients with pure mitral regurgitation, and 13 patients with combined lesions but dominant mitral regurgitation. Forty normal subjects were used as a control group. Twenty-one patients were studied after mitral valvulotomy for mitral stenosis.

2. The analysis of the filling phase of the apexcardiogram seems to give useful information regarding the presence of obstruction of the mitral valve. In patients with tight mitral stenosis, a rapid filling wave was not recorded in the apexcardiogram, and the filling angle (S) averaged 23°. The ratio T/S averaged 1.7.

3. Changes occurring after mitral valvulotomy suggest increased left ventricular filling, as revealed by the presence of a rapid filling wave in 19 patients after operation, with a filling angle (R) averaging 53°, compared with a mean S angle of 22° preoperatively.

4. In the group with pure mitral regurgitation, a rapid filling wave was present in all cases and averaged 64°, which was higher than that of the control group. Patients with mild or moderate mitral regurgitation presented R angles and ratios which were indistinguishable from those of the normal control group. Surgical lessening of mitral regurgitation resulted in the replacement of a preoperative rapid filling angle of 60° by a slow filling angle of 18°.

5. The duration of the rapid filling wave of the apexcardiogram in patients with mitral regurgitation indicates that increased regurgitation tends to shorten the rapid diastolic filling period.

6. Combined mitral valvular lesions clearly demonstrate the absence of a rapid filling wave when mitral stenosis is dominant, and its presence when mitral regurgitation dominates.

7. By this method, separation of patients with mitral regurgitation from normal subjects is possible only when severe degrees of regurgitation are present.

8. The Ry/V ratio correlated well with the filling wave of the apexcardiogram.

The operations were performed in most instances by Dr. F. C. Kittle. Several of our patients were referred for this special study from the Childrens Convalescent Center and by Dr. A. Diehl. We are indebted to the Audio-Visual Department of the KUMC and to Mrs. Natalie Razafsky for their technical assistance. Dr. W. Woodward, Dr. T. Andrews, and Dr. E. Crow helped in the analysis of the material.

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Intracardiac Infusion of Acetylcholine in Primary Pulmonary Hypertension

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The problem of vasomotion in the pulmonary vascular bed has been studied in many laboratories.[1-20] The purpose of this study is to investigate the effect of an intracardiac infusion of acetylcholine upon pulmonary arterial pressure in 2 patients with primary pulmonary hypertension.

MATERIALS AND METHODS

Right heart catheterization and puncture of the brachial artery were performed in the usual manner in the basal postabsorptive state. Cardiac output was determined by the direct Fick principle.

L. Fen., a 43-year-old white woman, was admitted to Mount Sinai Hospital in September, 1958. Exertional dyspnea had developed 8½ years prior to admission. Dizziness and weakness (without true syncope) were first noted in 1956. No other symptoms were present.

There was no history suggestive of pulmonary embolization. The patient had had one full-term normal pregnancy, preceded by several spontaneous abortions in the first 2 to 3 months of pregnancy, 12 years prior to admission.

The patient was a small woman, 56 inches tall, who weighed 80 pounds. The blood pressure was 148/80 mm. Hg, pulse rate 86 and regular, respiratory rate 18, and the temperature normal. Dyspnea, orthopnea, cyanosis, clubbing, edema, and distention of the neck veins were absent. The lungs were clear. The cardiac point of maximal impulse was in the fifth left intercostal space slightly outside the mid-clavicular line. Definite right ventricular and pulmonary arterial pulsations were palpable. The mitral first sound was louder than the mitral second sound. The pulmonic second sound was markedly accentuated and louder than the aortic second sound. All cardiac sounds were closely split. The degree of splitting did not vary with respiration. A Grade 3-4, harsh systolic murmur was heard in the third left intercostal space and was transmitted to the apex and aortic area. A Grade 2, high-pitched diastolic blow was heard at Erb's point.

The electrocardiogram revealed right ventricular hypertrophy. Cardiac fluoroscopy revealed good diaphragmatic motion. The lungs were clear. The transverse diameter of the heart was minimally increased. The aorta was small. The main pulmonary artery and its branches were markedly enlarged centrally; the peripheral pulmonary vascular markings were slightly diminished on an absolute basis and markedly diminished relative to the enlarged main pulmonary arteries. The left heart was normal. The right ventricle was markedly enlarged and the right atrium slightly enlarged.

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Supported by Grant H-4249 from the National Heart Institute.
Received for publication Jan. 15, 1960.

The initial impression was either (a) essential pulmonary hypertension, cor pulmonale, enlarged heart, normal sinus rhythm III D, or (b) congenital heart disease, Eisenmenger syndrome.

Right heart catheterization was performed on Sept. 16, 1958. The patient was discharged on oral digoxin and Priscoline after right heart catheterization. She was restudied in June, 1959, in order to determine the effects of therapy. Control observations were made at rest. Acetylcholine (5.0 mg./min.) was then infused into the right ventricular outflow tract before and during inhalation of 100 per cent oxygen.

M. J. Hol., a 44-year-old white woman, was hospitalized in March, 1959. Mild exertional dyspnea had been present for many years. She denied other cardiovascular symptoms. She had had two full-term normal pregnancies and deliveries, without any suggestion of pulmonary embolization.

The blood pressure was 140/86 mm. Hg, pulse rate 80 and regular, respiratory rate 16, and the temperature normal. Dyspnea, orthopnea, cyanosis, clubbing, edema, and distention of the neck veins were absent. The lungs were clear. The cardiac point of maximal impulse was outside the mid-clavicular line in the fifth intercostal space. There was no pulmonary arterial pulsation; a minimal right ventricular pulsation was present. The mitral second sound was greater than the mitral first sound and was markedly accentuated. The pulmonic second sound was also very loud and greater than the aortic second sound. The mitral, aortic, and pulmonic first sounds were closely split. No murmurs were noted.

The electrocardiogram revealed right ventricular hypertrophy. Cardiac fluoroscopy demonstrated normal lungs. The transverse diameter of the heart was increased. The aorta was small. The main pulmonary artery and its major branches were markedly enlarged. The peripheral pulmonary vascular markings were normal, but were relatively decreased in comparison to the enlarged central pulmonary vessels. The left heart was normal. The right ventricle and atrium were markedly enlarged. There was no hilar dance. The initial impression was idiopathic pulmonary hypertension, cor pulmonale, enlarged heart, normal sinus rhythm II C.

Right heart catheterization was performed after digitalization. Observations were made at rest and during exercise before and during infusion of acetylcholine (4.25 mg./min.) into the right ventricular outflow tract.

TABLE I. HEMODYNAMIC AND BLOOD OXYGEN DATA IN L. FEN. DURING THE FIRST CATHETERIZATION

	OXYGEN CONTENT (VOL. %)	OXYGEN CAPACITY (VOL. %)	% SATURATION	PRESSURE (MM. Hg)
I.V.C.	14.0			
S.V.C.	13.8			
High R.A.	12.4			
Low R.A.	13.9			2
Mid R.A.	13.3			2
Tricuspid R.A.	13.7			
Tricuspid R.V.	13.7			
Mid R.V.	14.1			122/5
Outflow R.V.	14.0			122/6
Main P.A.*	14.4			122/45, 75
R.P.A.	13.9			125/45, 78
R.B.A.	18.1	19.7	94	148/82, 109
L.A.	18.1	19.1	96	2

*Arteriovenous difference (M.P.A. and R.B.A.) = 3.7.

RESULTS

During the first catheterization in L. Fen., the tip of the catheter passed from the right to the left atrium. However, the left atrial sample was 96 per

cent saturated, and multiple blood samples from the right heart failed to reveal any evidence of a left-to-right shunt (Table I). It is most likely, therefore, that the tip of the catheter passed through a dilated foramen ovale rather than through a true atrial septal defect.

During the second catheterization, pulmonary arterial pressures were slightly higher, as were systemic pressures. The cardiac index averaged 2.98 L./min./M.^{2} at rest. Infusion of acetylcholine into the right ventricular outflow tract produced only a slight decrement in pulmonary arterial pressures, with a constant cardiac index, 2.99 L./min./M.^{2} (Fig. 1). Brachial arterial pressure was unchanged. Inhalation of 100 per cent oxygen during continued infusion of acetylcholine resulted in a further small decrease in pulmonary arterial pressure. The control mean pulmonary arterial pressure was 84 mm. Hg; the corresponding values during infusion of acetylcholine and inhalation of 100 per cent oxygen were 80 and 75 mm. Hg, respectively.

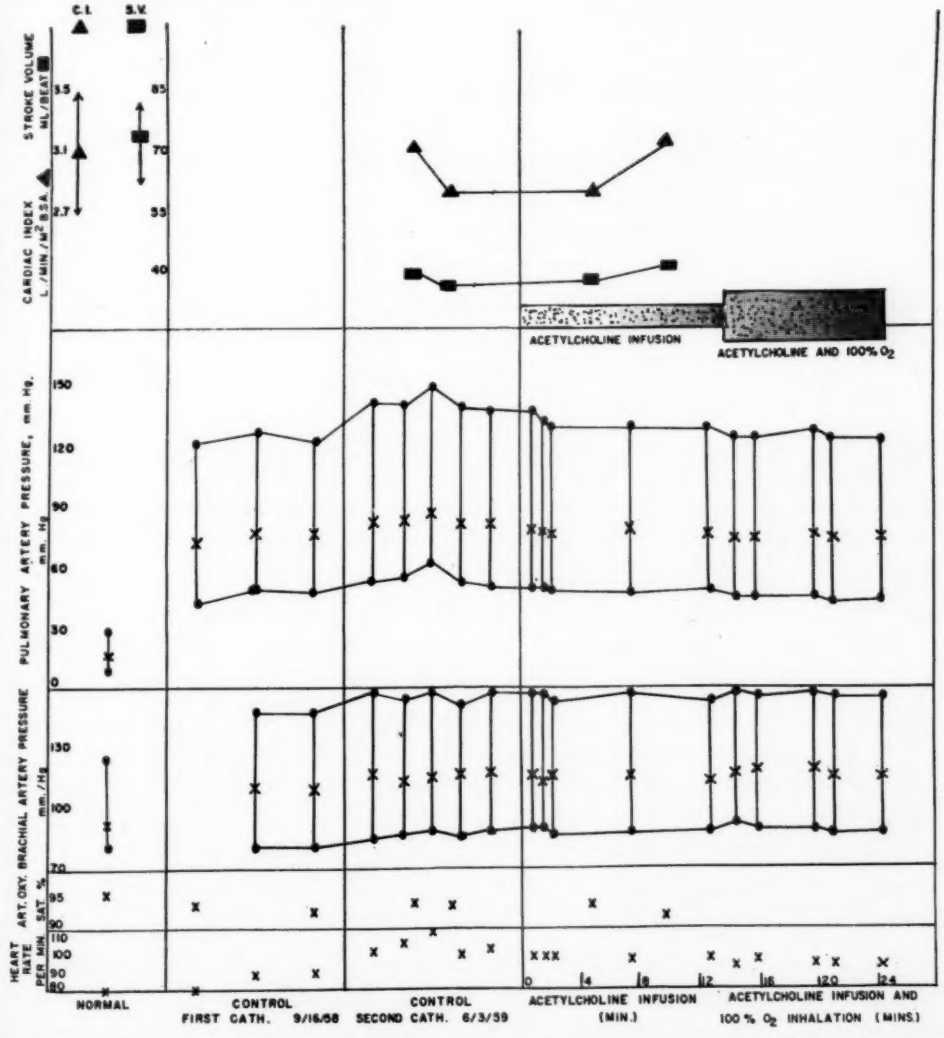

Fig. 1.—Hemodynamic data in L. Fen. during two cardiac catheterizations. Infusion of acetylcholine produced a small fall in pulmonary arterial pressure.

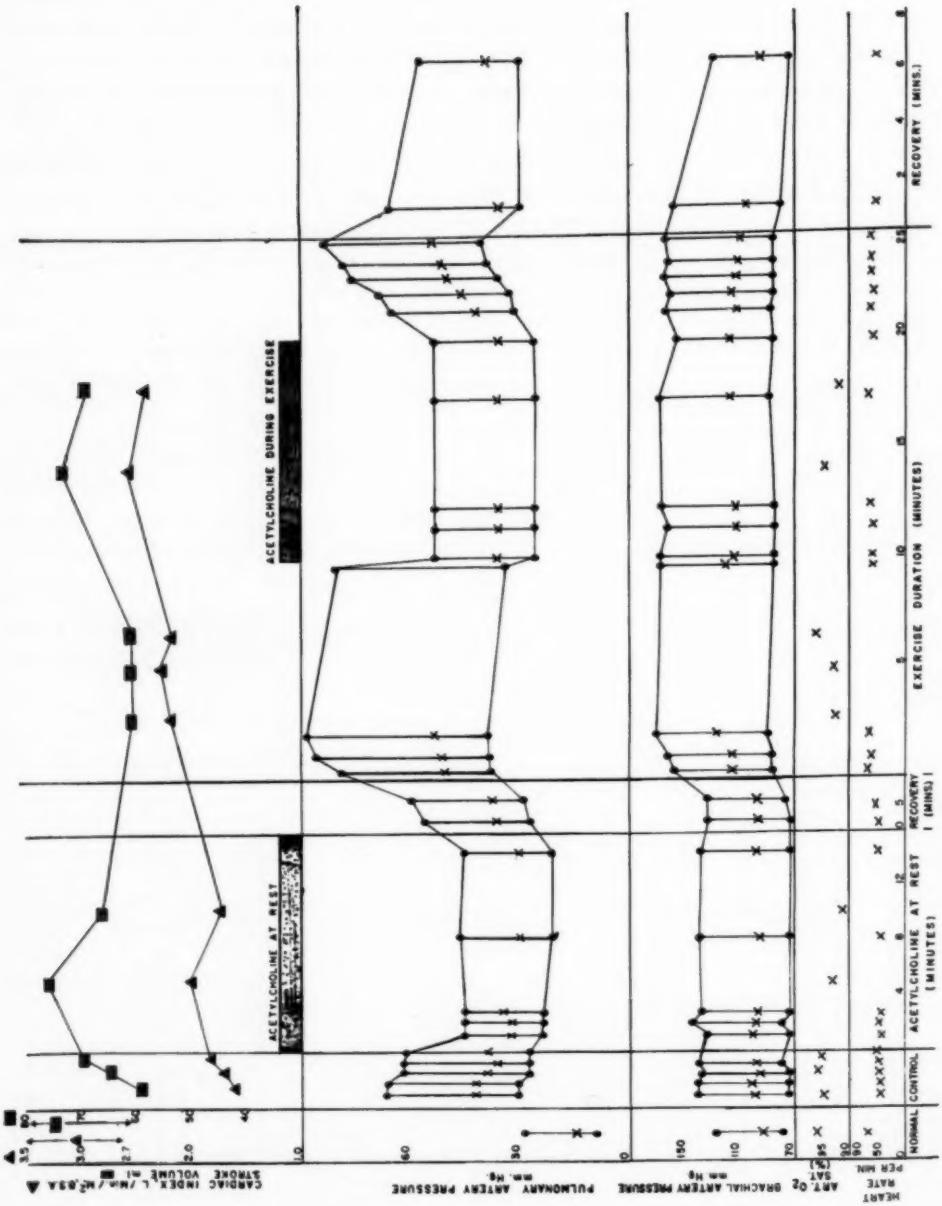

Fig. 2.—Hemodynamic data in M. J. Hol. Infusion of acetylcholine at rest and during exercise resulted in marked decrements in pulmonary arterial pressure.

The results of infusion of acetylcholine in M. J. Hol. were considerably more dramatic (Fig. 2). Moderately severe pulmonary hypertension, 61/28, 39 mm. Hg, was observed at rest; the cardiac index was 1.72 L./min./M.^{2}. Infusion of acetylcholine resulted in a sharp fall in pulmonary arterial pressure, to 47/21, 30 mm. Hg; the cardiac index rose slightly to 1.87 L./min./M.^{2}. During exercise, pulmonary hypertension increased sharply to 85/37, 55 mm. Hg. Infusion of acetylcholine during continued exercise caused a gross decrement in pressure to 53/26, 35 mm. Hg, despite a slight increase in output. Infusion of acetylcholine was stopped while exercise continued, and within 4 minutes the pulmonary arterial pressure rose to 84/41, 54 mm. Hg.

DISCUSSION

Catheterization of the right side of the heart dates back almost 20 years.[21] Initially, the concept of vasomotor activity in the pulmonary vascular bed was denied. More recently, evidence has accrued to support the thesis of pulmonary arterial vasoconstriction and vasodilation. Fritts and Cournand[22] have reviewed the evidence for vasoconstriction and have discussed the factors other than vasoconstriction or vasodilation which can modify the level of pulmonary arterial pressure. These include: "(1) Rate of pulmonary blood flow. (2) Heart rate. (3) Pressure in the left atrium. (4) Constriction or dilation in the systemic circulation. (5) Extravascular pressure within the alveoli and thorax. (6) Central blood volume." It is difficult to keep all these variables constant during studies in man.

Recent interest in pulmonary vasodilation in man has centered on acetylcholine.[8-10,12] Rapid inactivation of this drug in the blood stream (Duff and associates,[23] and Tiffeneau and Beauvallet[24]) prompted Harris[8] and Wood[9] to study the effects of injection of acetylcholine into the right heart in patients with varied types of heart disease. Both investigators injected single doses rapidly through the cardiac catheter. A dose large enough to dilate the pulmonary vascular bed yet small enough to be inactivated by the time it reached the systemic circulation (to prevent systemic hypotension) was employed. Fritts and associates[18] infused acetylcholine at a constant rate into the right heart of normal subjects under control and hypoxic conditions. It was concluded that acetylcholine caused pulmonary vasodilation especially during hypoxia.

Pulmonary vasoconstriction has been advanced as one possible mechanism for the pulmonary hypertension in primary pulmonary hypertension.[1,25] Therefore, the effect of intracardiac infusion of acetylcholine would be of great interest. The administration of other agents, such as Priscoline, hexamethonium, and reserpine, and stellate ganglionic block and upper thoracic sympathectomy had proved disappointing in demonstrating a consistent pulmonary vasodilation effect in patients with primary pulmonary hypertension.[1]

Harris[8] made observations during intracardiac injections of a single dose of acetylcholine in 3 patients with primary pulmonary hypertension. In one patient a fall in pulmonary arterial pressure of 13 mm. Hg systolic and 5 mm. Hg diastolic was noted; in another patient the decrement in pressure was 20 systolic and 15

diastolic. In the third patient the pulmonary arterial pressure was unchanged after acetylcholine. Wood[10] has made corresponding observations by injecting single doses of acetylcholine in 6 patients with primary pulmonary hypertension. In 5 patients, pulmonary arterial pressure fell. The average decrease in pulmonary arterial systolic pressure was 30 mm. Hg. Marshall and co-workers[26] infused acetylcholine into the right ventricle at a rate of 2.0 mg./min. in a patient with primary pulmonary hypertension. Pulmonary arterial mean pressure fell from 56 to 25 mm. Hg while the subject inhaled air. A fall of similar magnitude was observed when the infusion of acetylcholine was repeated during inhalation of 100 per cent oxygen.

The observations on L. Fen. and M. J. Hol. were made during a constant drip infusion of acetylcholine into the right ventricular outflow tract. The fall in pulmonary arterial pressure in M. J. Hol. was pronounced (Fig. 2) both at rest and during exercise. It must be emphasized that these changes occurred without decreases in systemic arterial pressure and cardiac output, and thus suggest pulmonary vasodilatation. On the other hand, acetylcholine produced a fall in pulmonary arterial pressure of lesser magnitude in L. Fen.

In both patients the decrements in pulmonary arterial systolic pressure during infusion of acetylcholine were of greater magnitude than the decreases in both diastolic and mean pressures. The magnitude of the fall in pulmonary arterial pressure in M. J. Hol. suggests that the vasoconstrictive factor was of primary importance in the maintenance of the pulmonary arterial hypertension, and is in keeping with the thesis that the disease process was less advanced than in L. Fen. In the latter patient, the degree of pulmonary hypertension and the more limited response to infusion of acetylcholine are both probably due to the superimposition of pulmonary vascular disease upon the vasoconstrictive factor. Although the effect of inhalation of 100 per cent oxygen per se on pulmonary arterial pressure was not studied in these two patients, Shepherd and co-workers[27] observed only a slight decrease in mean pulmonary arterial pressure (average decrement, 1.5 mm. Hg) in 8 patients with primary pulmonary hypertension during the breathing of 100 per cent oxygen.

SUMMARY

Two cases of primary pulmonary hypertension are presented, and the results of right heart catheterization are given. Infusion of acetylcholine caused large decreases in pulmonary arterial pressure in one subject, both at rest and during exercise. In the second subject, infusion of acetylcholine resulted in a lesser but still significant decrease in pulmonary arterial pressure. The criteria that must be met before conclusions are drawn as to the existence of vasodilatation or vasoconstriction in the pulmonary vascular bed are discussed.

We are indebted to Stanley Dzwonkowski, B. A., and William Oliver, B. S., for technical aid.

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Untoward Effects of Rapidly Administered Intravenous Acetylcholine During Studies of the Circulation Time

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There is a need for a simple bedside method of measurement of circulation time which would provide an objective and reproducible end point. Acetylcholine (Ach) has been studied in dogs as an agent for the determination of circulation time.[1] Its effect on the heart rate and the P-R interval provided an objective end point and a permanent electrocardiographic record. Therefore, acetylcholine seemed to be a very desirable agent for clinical use. The safety of rapid intravenous administration of acetylcholine in human subjects has been well documented.[2,3]

We have compared acetylcholine with two other agents commonly used for the determination of circulation time, Decholin and sodium succinate,*[4] in 5 healthy men, 24 to 28 years old. The results of our brief experience are reported.

METHODS

The subjects, 4 medical students and 1 physician, rested supine, with an 18-gauge needle, attached to a three-way stopcock, inserted in an antecubital vein. A solution of 5 per cent dextrose in water was slowly infused before and between the injections of tested substances, which included: (1) 3 c.c. of Decholin, (2) 2 c.c. of sodium succinate, and (3) 10 to 40 mg. of Ach dissolved in 5 per cent dextrose with water in a concentration of 10 mg./ml. The Ach solution was prepared by injection of 10 ml. of 5 per cent dextrose in water into a vial containing 100 mg. of anhydrous Ach powder. The diluent was mixed well by flushing the solution in and out of the syringe several times. Each milliliter of solution contained 10 mg. of Ach. A syringe containing atropine solution was attached to the third outlet of the stopcock in order to counteract the undesirable effects of Ach.

In 2 subjects, each agent was injected three times, and the order of the injection was changed each time. In 4 subjects in whom the initial dose of 10 mg. of Ach failed to produce an end point, the doses were increased by 10 mg. at a time until a satisfactory end point was obtained. The largest dose of Ach was 40 mg.

RESULTS

All subjects reported that they sensed the taste of Decholin several seconds before they were able to communicate this information. After injection of sodium succinate, all subjects felt a warmth in the throat several seconds before they coughed or swallowed.

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Supported by a grant from the Vermont Heart Association.

Received for publication Jan. 18, 1960.

*Soduxin (Brewer Co., Worchester, Mass.).

The end point of Ach was considered to be the time of the onset of QRS of the complex preceding the first prolonged R-R interval (Fig. 1). When the increase in the R-R duration was not abrupt but gradual, the end point could not be determined with confidence (Fig. 2), and a larger dose was administered. The results are summarized in Table I.

It can be seen that an end point could be obtained with Ach in all tested subjects, but that it frequently required several trials. One can further see that in 2 subjects in whom two or three determinations were made the results were reproducible. This was not true of the results with Decholin and sodium succinate. The circulation times measured with Ach were significantly shorter than the circulation times measured with other agents. The injection of Ach caused in nearly all instances a discomfort along the course of the vein.

In Subject A, asystole lasted for 3 seconds, and he experienced mild substernal discomfort; the asystole was followed by nodal rhythm for 14 seconds. In Subject E, asystole lasted for 6 seconds, was followed by one sinus beat, then another period of asystole for 3.6 seconds, again a single sinus beat and another asystole for 10.6 seconds, followed by a nodal escape rhythm with retrograde conduction to the atrium for 6 seconds. During the last period of asystole, Subject E had a brief, generalized convulsive seizure accompanied by involuntary micturition. Atropine was injected promptly, but it seems unlikely that it could have reached the heart during asystole. Episodes of this type could probably be obviated if the patient was connected during the test to an artificial cardiac pacemaker.

Our experience contrasts with that of Segers and co-workers[2] and Arnulf,[3] who failed to observe serious untoward effects during rapid intravenous administration of Ach. Segers and co-workers injected a 2 per cent solution of Ach in water as rapidly as possible in about 40 subjects (predominantly patients with heart disease) about 250 times. They emphasize the variations in individual

TABLE I. CIRCULATION TIME IN SECONDS

SUBJECT	DECHOLIN	SODIUM SUCCINATE	ACETYLCHOLINE				UNTOWARD EFFECTS OF ACH
			10 MG.	20 MG.	30 MG.	40 MG.	
A	——	15	—	—	—	8	Nodal rhythm. Substernal pressure
B	14	15	NEP	NEP	6.5	—	—
C	15 16.5 16	16 18 18.5	NEP	NEP	9.3 NEP NEP	—	—
D	19 19 23	24.5 29 35	NEP	NEP	10	10 10	—
E	18.5	22 28	NEP	5.8 5.6	—	—	Nodal rhythm. Asystole for 10.6 sec. Convulsion

NEP: No end point.

tolerance to Ach and advocate an initial dose of 20 mg., followed by increments of 20 mg. These authors mention instances of cardiac standstill which lasted from 5 to 15 seconds after the administration of doses ranging from 50 to 200 mg. It appears that some instances of Adams-Stokes seizures were encountered, but the doses responsible for these episodes are not stated, and emphasis is put on the fact that all individuals returned to their normal state several minutes after the end of the injection. Segers and co-workers quote the experience of Fiamberti, who rapidly injected 600 mg. of Ach 4,000 times in 120 patients with schizophrenia. These doses caused unconsciousness and convulsive seizures in all patients, but no fatalities or permanent sequelae were encountered. Arnulf[3] injected rapidly 150 to 300 mg. of Ach in adult patients subjected to coronary arteriography. This dose produced a cardiac standstill which lasted from 4 to 12 seconds.

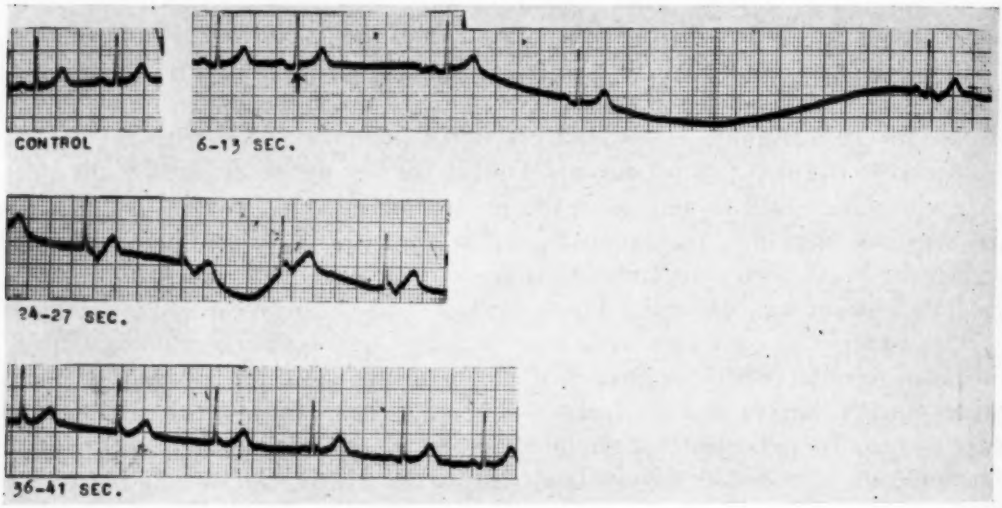

Fig. 1.—The arrow points at the QRS complex preceding the first prolonged R-R interval. Note the nodal escape rhythm in the second strip and the reappearance of the sinus rhythm in the third strip. Time in seconds (sec.) after injection of Ach.

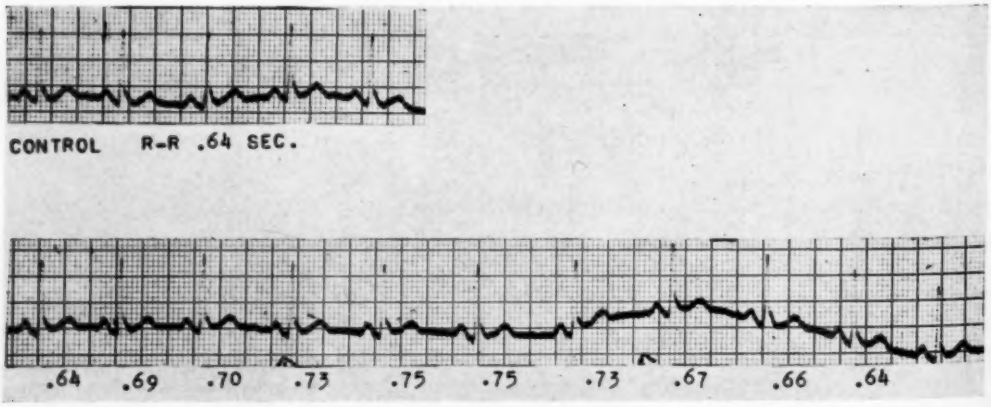

Fig. 2.—The lower strip illustrates absence of a sharp end point 5 to 10 seconds after injection of 20 mg. of Ach. Note that the duration of the R-R interval increases gradually.

In the course of 26 coronary arteriographies there were no incidents, but in order to avoid subjective complaints the procedure was performed under general anesthesia with pentobarbital and tracheal intubation. Kozhucharov[7] reports an episode of cardiac standstill which lasted from 10 to 15 seconds and was accompanied by a syncope in a patient treated for paroxysmal atrial tachycardia with 150 mg. of Ach intravenously.

The untoward side effects encountered by us with small doses may possibly be caused by an unusual susceptibility of our subjects. However, the mere fact that such accidents occur in healthy individuals suggests that the rapid intravenous administration of small doses of Ach in individuals with myocardial or cerebral ischemia may lead to very serious complications.

The short circulation times obtained with Ach are of interest. On the basis of experience with dogs,[1] one must assume that these circulation times represent the time of passage of blood from the arm to the coronary capillaries supplying the sinus node. The fact that the circulation time with Decholin and sodium succinate was so much longer in the subjects studied by us can probably be accounted for by a longer circulatory pathway and relatively complicated transmission system as well as a delay between sensing the tested agent and reacting to it. In addition, there is a possibility that the decrease in pulmonary vascular resistance which may occur after the administration of Ach[5] actually causes some shortening of the circulation time.

The appearance of nodal rhythm in 2 subjects in whom asystole lasted for several seconds suggests that the A-V node is less sensitive to the action of Ach than are the sinus node or the sinoatrial conduction system. In these subjects the retrograde conduction through the atrium was preserved, whereas the forward conduction was apparently blocked. A similar observation of the effect of Ach on conduction between the A-V node and the bundle of His has been reported recently.[6]

Conclusion.—Although the intravenous administration of acetylcholine (Ach) in man appeared to give sharp and reproducible end points, it could not be used safely for clinical determinations of circulation time.

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Effects of Hyaluronidase Upon the Distribution of Plasma Albumin and Red Blood Cells in Normal and Ischemic Myocardium

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With the Assistance of Martin I. Schock

Previous studies have demonstrated that the intravenous administration of hyaluronidase reverts some of the electrocardiographic alterations found in clinical and experimental coronary artery occlusion.[1] This enzyme also prevents the significant increase in water content in the ischemic myocardium following experimental ligation of a major coronary artery.[2] In the present study, the effects of hyaluronidase upon the distribution of I^{131}-labeled plasma albumin and Cr^{51}-labeled erythrocytes in the normal and ischemic myocardium have been ascertained in an effort to gain some insight into the mechanism of action of this spreading factor in experimental coronary occlusion.

MATERIAL AND METHODS

Sixteen dogs of both sexes were used; they weighed from 7 to 17 kilograms. After intravenous administration of pentobarbital sodium (30 mg./Kg.), the femoral artery and vein were isolated, and a thoracotomy was performed. All animals were kept under artificial respiration during the entire procedure. At the beginning of each experiment, 50 μc of I^{131}-labeled plasma albumin and 400 μc of Cr^{51}-labeled erythrocytes were injected into the femoral vein. The red blood cells were labeled after the method of Sterling and Gray.[3] An hour later, the left circumflex coronary artery was ligated in 12 dogs. In the other 4, no ligature was placed (controls). Six of the dogs in which the circumflex artery was ligated received 100,00 units of hyaluronidase* in 10 ml. of saline intravenously immediately after ligation and at hourly intervals until the end of the experiment. The other 6 animals which underwent ligation received no enzyme. The 4 control dogs were killed 2 hours after the isotopes had been injected. All of the other animals were sacrificed at the end of 5 hours after coronary ligation. A random sequence was employed in conducting the various experimental and control procedures.

Five to 10 minutes prior to the time of sacrifice, blood was collected from the femoral artery for the determination of hematocrit ratio and radioactive isotope content. The heart was removed immediately after death and briefly washed with tap water. This organ was then opened, and samples of the posterior papillary muscle (PPM) and of the anterior superior zone of the left

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This investigation was supported by Research Grant H-3464 from the National Heart Institute.
Received for publication Jan. 22, 1960.
*Supplied through the generosity of Wyeth Laboratories, Philadelphia, Pa.

ventricular wall (ASLV) were removed. The reasons for the choice of these regions have been explained previously.[2] It will suffice to state here that, in the experiments in which the circumflex artery was ligated, PPM represents an ischemic area, and ASLV a normal one. The samples of myocardium were placed in previously tared plastic tubes, and their weights were determined to the nearest 0.1 mg. Finally, the specimens of myocardium, as well as 1 ml. of the diluted arterial blood, were counted in a well-type scintillation counter (initial counts). The counts were repeated 14 days later (final counts). Since Cr^{51} and I^{131} decay at different rates, the blood and tissue content of each isotope may be determined from the total gamma emissions determined at two different points in time.

Calculations of Total Blood, Plasma and Red Cell Content in PPM and ASLV.—

(1) $$Cr^{51} = \frac{N_t - aN_o}{b - a}$$

$$I^{131} = N_o - Cr^{51}$$

Cr^{51} = counts due to Cr^{51} in blood or tissue; I^{131} = counts due to I^{131} in blood or tissue; N_o = total counts at time o; N_t = total counts at time t; a = fraction of I^{131} remaining at time t (a = 0.2973 at t = 14 days); b = fraction of Cr^{51} remaining at time t (b = 0.6933 at t = 14 days)

(2) $$\text{ml. whole blood/Gm. tissue} = \frac{Cr^{51}/\text{Gm. tissue}}{Cr^{51}/\text{ml. blood}}$$

(3) ml. erythrocytes/Gm. tissue = hematocrit × ml. whole blood/Gm. tissue

(4) ml. intravascular plasma/Gm. tissue = (2) − (3)

(5) $$\text{ml. total plasma/Gm. tissue} = \frac{(I^{131}/\text{Gm. tissue}) \times (1.00\text{-hematocrit})}{I^{131}/\text{ml. blood}}$$

(6) ml. extravascular plasma equivalent/Gm. tissue = (5) − (4)

Assumptions.—Equation (4) is dependent upon the assumption that Cr^{51} is located entirely within the intravascular compartment. The isotope is rather tightly bound to the red cells, so that only a negligible fraction separates within the time limits of an experiment.[3] Also, pathologic studies have revealed very little extravasation of erythrocytes into the ischemic zone within 5 hours after coronary occlusion.[4,5]

Equations (2), (4), and (6) are all dependent upon the assumption that the hematocrit ratio is constant throughout the vascular system within the myocardium. It is very probable, however, that the hematocrit ratio of the blood within the smaller vessels is somewhat less than the value in arterial blood.[6] This has not been corrected for in our computations, since the precise value of the mean hematocrit ratio for the blood within the myocardial bed is not known. In the control experiments, the true intramyocardial hematocrit ratios are probably virtually identical in the regions studied. With coronary artery ligation, however, the ratio is probably somewhat higher in the ischemic zone, since the hematocrit ratio is an inverse function of the velocity of flow in small tubes.[6]

In Equations (5) and (6) the term "plasma" does not necessarily imply a fluid identical in composition with arterial plasma. Since its value is derived from the tissue content of I^{131}-labeled albumin, "plasma" actually refers to the volume of arterial plasma which would contain the measured amount of I^{131}. Especially with respect to the interstitial compartment, the "plasma" volume serves as a useful index of plasma albumin content.

RESULTS

The data obtained from the dogs in which a coronary artery was not ligated (controls) are presented in Table I. It is evident that no significant difference ($p = 0.5$) exists between the blood, red cell, intravascular plasma, and extravascular plasma equivalents in the two standard myocardial zones (ASLV and PPM).

Fig. 1 illustrates the content of whole blood, red cells, intravascular and extravascular plasma equivalents, and water in a normal (anterior superior left ventricle) and an ischemic (posterior papillary muscle) zone of myocardium, in untreated animals and in dogs receiving intravenous injections of hyaluronidase. The values for the normal nontreated region (ASLV) 5 hours after ligation of the circumflex branch are identical to those obtained from both regions (ASLV and PPM) of the control dogs.

From this figure it becomes evident that ischemia, hyaluronidase, or the combination of both, do not exert any important influence upon the normal content of whole blood, red cells, or intravascular plasma ($p > 0.2$). Ischemia does produce a marked increase in the extravascular plasma equivalents and water content,* as compared to the normal region ($p < 0.01$). In the nonischemic myocardium, hyaluronidase also increases the extravascular plasma equivalents ($p < 0.01$), but does not exert any effect upon the water content. In the ischemic zone, hyaluronidase does not affect the extravascular protein content to a statistically significant degree, but it does effectively prevent the large increase in water content observed in the untreated ischemic myocardium.

TABLE I. CONTENT OF RED CELLS AND PLASMA IN THE ANTERIOR SUPERIOR LEFT VENTRICLE AND POSTERIOR PAPILLARY MUSCLE OF CONTROL DOGS

	ASLV (C.C./GM. OF TISSUE) MEAN ± S.E.	PPM (C.C./GM. OF TISSUE) MEAN ± S.E.
Total blood	0.0360 ± 0.0026	0.0357 ± 0.0027
Red cells	0.0152 ± 0.0020	0.0148 ± 0.0018
Intravascular plasma	0.0208 ± 0.0019	0.0209 ± 0.0020
Extravascular plasma equivalents	0.0250 ± 0.0015	0.0243 ± 0.0012

DISCUSSION

Anoxia is certainly a major factor in the pathophysiologic mechanism of the alterations which follow coronary artery occlusion. The decrease in oxygen tension not only brings about damage to the cells, but also produces an increase in capillary permeability.[7] This is confirmed by the increase in extravascular plasma equivalents, which is here expressed by an elevation of the I^{131}-labeled plasma albumin content (Fig. 1). As a consequence of the augmented oncotic pressure in the interstitial spaces, a large amount of water is found in the ischemic areas. In addition, because of an electrolyte disequilibrium in the regions affected by anoxia, a certain amount of water may also go into the cells.

The absence of significant alterations in the cellular and plasma content of the intravascular compartment in the damaged regions may be accounted for by invoking divergent mechanisms: (1) Beyond the arterial ligature the intravascular pressure decreases. This tends to decrease the blood volume. (2) On

*Most of the data which represent water content in this study have been obtained from previous work.[3]

the other hand, as a consequence of ischemia, there is a reduction of vasomotor tone in the damaged area. This tends to increase the blood volume. If these two antagonistic effects were approximately equal in magnitude, it would account for the absence of any change in the intravascular red cells or plasma content following ligation.

Having thus established the effects of ischemia, it now becomes possible to analyze the influence of hyaluronidase upon the red cells, plasma, and water content in normal and ischemic myocardium. From our observations concerning the effects of hyaluronidase upon normal tissue, two conclusions may be drawn: (1) Hyaluronidase enhances the transport of plasma proteins from the vessels to the interstitial fluid, indicating an increase in capillary permeability. This is in agreement with the findings of Szabo and Magyar,[8,9] who described an increase in plasma protein concentration in the lymphatics after the intravenous administration of hyaluronidase. (2) No significant changes are observed in the water content of myocardial tissues. Of course, an increase in the transfer of water from

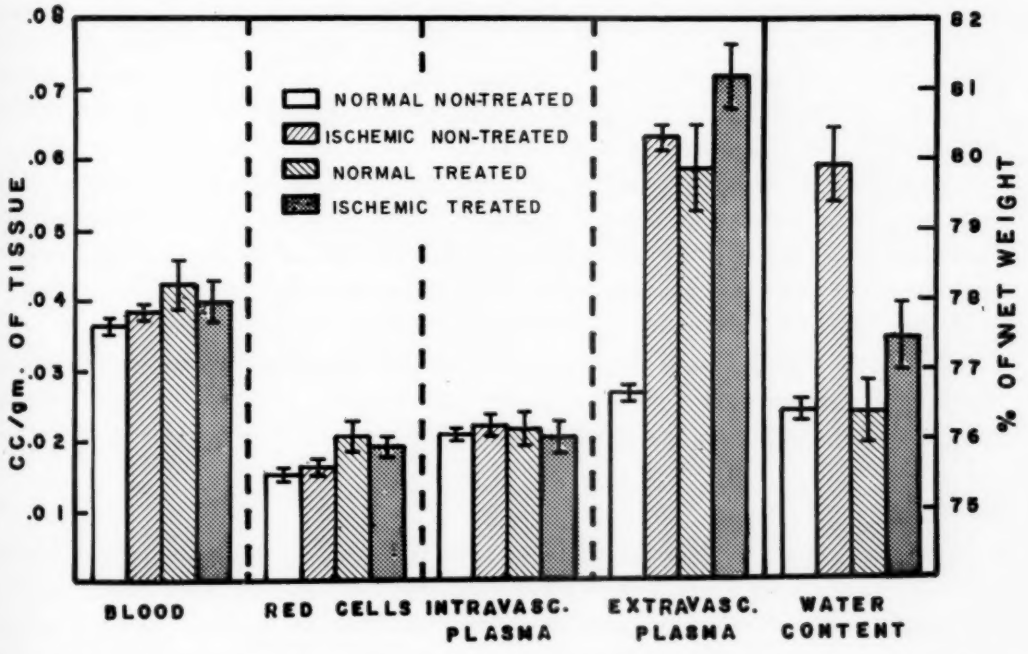

Fig. 1.—The content of whole blood, red cells, intravascular and extravascular plasma equivalents, and water in normal and ischemic myocardium of untreated animals, and of those receiving hyaluronidase. The height of each column represents the mean value, and the length of the vertical lines, the standard errors.

the vessels to the extravascular compartment is expected to occur as a consequence of the increased transport of plasma proteins. The reasons that the water content remains unchanged may be found in the effects of hyaluronidase upon the viscosity of the ground substance.[10] By decreasing viscosity, this enzyme allows a faster diffusion of water throughout the mesenchyme, thereby facilitating its reabsorption by the lymphatics. The proteins of the plasma diffuse at a much slower rate, thus remaining in larger amount, for a longer period of time, in the interstitial

spaces. We are dealing, therefore, with a substance that, although increasing capillary permeability, does not give rise to an accumulation of water in the extravascular compartment. This was anticipated by Hechter[11] in 1950. At that time, he stated that "if a substance increases capillary permeability to protein, localized edema need not result if the excess fluid which enters the tissue is rapidly removed via the lymphatics."

The effects of hyaluronidase upon a myocardial tissue rendered ischemic as a consequence of coronary artery ligation are represented in Fig. 1. It is observed that, although the amount of plasma proteins increases still more in the extravascular compartment, the water content decreases to values much lower than those found in ischemic areas not submitted to the effects of the enzyme. This must also be dependent upon the disproportional rates of diffusion of water and plasma proteins.

When the effects of hyaluronidase upon normal and ischemic tissues are compared, it becomes evident that this enzyme reduces water content only when the water content was previously elevated. Such a fact is in agreement with the studies of Hechter,[11] who demonstrated that hyaluronidase decreases edema only if tissue volume and pressure are increased. This is exactly what occurs in ischemic myocardial regions in which the amount of water is elevated and, thereby, local pressure is augmented.

Our present findings sustain previous observations upon the existence of intramyocardial edema in ischemic areas[2,12-14] and, to a certain extent, define its pathogenesis. They also confirm two important effects of hyaluronidase: (1) an increase in capillary permeability, and (2) a reduction in the water content in tissues in which this water content was previously elevated.

Until the role played by intramyocardial edema in the evolutive process of coronary artery occlusion can be totally ascertained, our results must remain confined to the experimental field, as guide for further investigations.

SUMMARY

The effects of hyaluronidase have been determined upon the whole blood, red cell, intravascular and extravascular plasma equivalents, and water content of normal and ischemic myocardium of the dog. Neither ischemia nor hyaluronidase, alone or combined, affects the myocardial content of red cells or intravascular plasma. Ischemia produces a marked increase in the water content and extravascular plasma equivalent, presumably as a result of increased capillary permeability. Hyaluronidase also increases the extravascular plasma equivalent, but not the water content, of the normal myocardium. In a region rendered ischemic as the result of coronary artery ligation, the increase in water content is largely prevented by the hourly intravenous injection of hyaluronidase. It is concluded that this enzyme reduces localized edema after coronary ligation by virtue of its actions as a spreading factor and as a lymphagogue.

The authors wish to express their appreciation for the valuable assistance of Dr. E. J. O'Malley and Dr. E. J. McCaffrey in the determination of radioactive counts.

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Inhibition of Experimental Myocardial Necrosis by the Monoamine Oxidase Inhibitor Isocarboxazid (Marplan)

Gerhard Zbinden, M.D., Nutley, N. J.

In 1957, Cesarman[2] first reported that the monoamine oxidase (MAO) inhibitor, 1-isonicotinyl-2-isopropylhydrazine (iproniazid*), has a pronounced analgesic effect on chest pain in patients with angina pectoris. This observation has been confirmed by many investigators,[3,5,7,10,12] and it has been shown that other MAO inhibitors, chemically related to iproniazid, also diminish the intensity and frequency of anginal pain and the need for nitroglycerin.[6,9,11] Based on clinical or experimental evidence, various explanations for the mode of action of these drugs were proposed, [14] but none of these theories has been generally accepted. In most clinical cases reported so far, no improvement was noted on the ECG, and it was therefore concluded that these drugs acted probably by stimulation of the central nervous system or on the transmission of pain. In this paper, animal experiments are described which indicate that MAO inhibitors may have an "oxygen-sparing" effect on the heart muscle.

TABLE I. AVERAGE DEGREE OF CARDIAC NECROSIS IN GROUPS OF 8 RATS EACH TREATED WITH ISOPROTERENOL

GROUP	PRETREATMENT WITH ISOCARBOXAZID INTRAPERITONEALLY FOR ONE WEEK (MG./KG.)	ISOPROTERENOL—TWO SUBCUTANEOUS INJECTIONS (MG./KG.)	HISTOLOGICALLY ESTIMATED DEGREE OF MYOCARDIAL NECROSIS (AVERAGE)	PROBABILITY p
1	50	80	1.7	<.001
2	—	80	3.5	—
3	50	80	1.8	<.001
4	—	80	4.0	—
5	50	2	1.6	<.001
6	—	2	2.8	—
7	50	2	1.6	<.001
8	—	2	3.3	—
9	30	50	2.4	<.02
10	—	50	3.6	—
11	—	—	0	—

From the Biological Research Department, Hoffmann-La Roche Inc., Nutley, N.J.
Received for publication Feb. 3, 1960.
*Marsilid.

METHODS

Five groups of four female and four male rats of the Holtzman strain, weighing from 180 to 250 grams, were pretreated with daily intraperitoneal injections of 50 mg. or 30 mg. per kilogram of 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine* (isocarboxazid) for one week. On the following two days, the animals received subcutaneous injections of 2, 50, or 80 mg./Kg. of 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol (isoproterenol). Five additional groups of 8 rats each, not pretreated with isocarboxazid, were injected with the same doses of isoproterenol on two consecutive days. A control group of 8 animals received no treatment at all (see Table I). Twenty-four hours after the second injection of isoproterenol, all rats were sacrificed. The hearts were washed in saline and fixed in Zenker's solution. Two identical parts of the left ventricle of each heart were imbedded in paraffin, cut for histologic examination, and stained with hemalaun-eosin. Myocardial necroses were observed in all but the control rats. Severity and extent of the necroses were rated with 1+ to 5+, and the average degree of myocardial necrosis of each group pretreated with isocarboxazid was compared with that of the corresponding group not injected with this compound but treated with the same dose of isoproterenol. The t-test of Student was used for statistical evaluation.

Fig. 1.—Focal myocardial necrosis induced in rats by two injections of 80 mg./Kg. of isoproterenol (×256, reduced ⅓; hemalaun-eosin).

RESULTS

Infarct-like myocardial lesions produced in rats by subcutaneous injections of isoproterenol were recently reported by Rona and co-workers.[8] In practically all rats injected with 1 mg. per kilogram of isoproterenol or more on two consecutive days, cardiac necroses, commonly located in the apical area of the left ventricle, were observed. These results were confirmed in our experiments. Even though it was sometimes difficult to detect the necroses by gross observa-

*Marplan.

tion, because in mild cases the subendothelial fibers were predominantly affected, the histologic examination always revealed the typical infarct-like lesions which were variable in size and number. By rating the severity and extent of the histologically detectable lesions (Table I), it was evident that the necroses observed in the animals pretreated with isocarboxazid were much less marked and less frequent than those in the corresponding groups which had not been previously injected with this drug. In all five experiments, the difference was statistically highly significant. The histologic picture, however, which is characterized by hyalin necrosis and disintegration of muscle fibers, mild to moderate infiltration with leukocytes and histiocytes, interstitial edema, and dilation of the capillaries (Fig. 1), was similar in all animals, whether pretreated with isocarboxazid or not.

DISCUSSION

According to Rona and co-workers,[8] the cardiac necroses produced in rats by repeated injections of isoproterenol are probably due to transient fall in blood pressure and an increased oxygen requirement of the myocardial tissue. Inhibition of MAO does not alter the cardiovascular effect of isoproterenol.[4] Thus, it is possible that the marked inhibition of myocardial necroses observed in animals pretreated with isocarboxazid is due to a decreased oxygen requirement, the mechanism of which is not known. Todd and co-workers[13] have reported that iproniazid protected animals against anoxic organ damage induced by different experimental methods. These observations also indicate that MAO inhibitors may influence oxidative processes, and it seems worth while to further investigate this possibility in experimental animals as well as in patients with angina pectoris.

SUMMARY

Pretreatment with the monoamine oxidase inhibitor isocarboxazid partly inhibits cardiac necroses induced in rats by subcutaneous injections of isoproterenol.

The author wishes to acknowledge the technical assistance of Mr. V. Augulis, Mrs. A. Oberhänsli, and Miss E. Tschuschke.

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Case Reports

Venous Air Embolism Complicating Angiocardiography: An Illustrative Case Report

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During angiocardiography, performed because of suspected pulmonary vascular disease in a 35-year-old man, the combination of upright posture and a faulty or improperly closed stopcock allowed the entry of approximately 40 c.c. of air into the venous system. Its accumulated presence in the upper venous

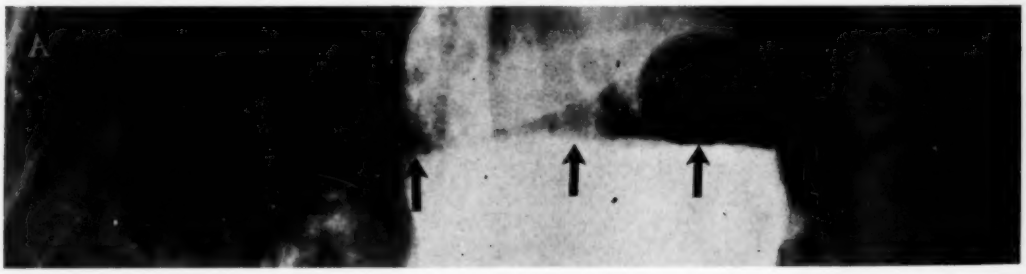

Fig. 1*A*.—Two and one-half seconds after the beginning of the injection of 40 c.c. of contrast agent and a similar amount of air (see text). Horizontal air-fluid line traverses both main pulmonary arteries.

tributaries of the right atrium was unrecognized until the force of the angiocardiographic injection propelled it into the right heart. Seconds later, the patient complained of a strange sensation in the chest. Placed in the recumbent position, he became pulseless, cyanotic, and unconscious. An ear to the chest established the nature of the complication. The patient was turned on his left side, and immediately the peripheral pulses reappeared; there was a gradual return of consciousness during the succeeding 15 minutes. A severe headache

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This work, done in the Minthorne Memorial Lab for Cardiovascular Research Through Radiology, was supported by grants from the United States Public Health Service (H-3275 [C2]), the Oregon Heart Association, and the Mallinckrodt Chemical Works.

Received for publication Jan. 25, 1960.

persisted for an hour, but recovery was otherwise complete. Angiocardiographic exposures (Fig. 1), 2½ and 4 seconds after the beginning of the injection, revealed gas filling the upper third, and contrast agent the lower two thirds, of the pulmonary arterial tree.

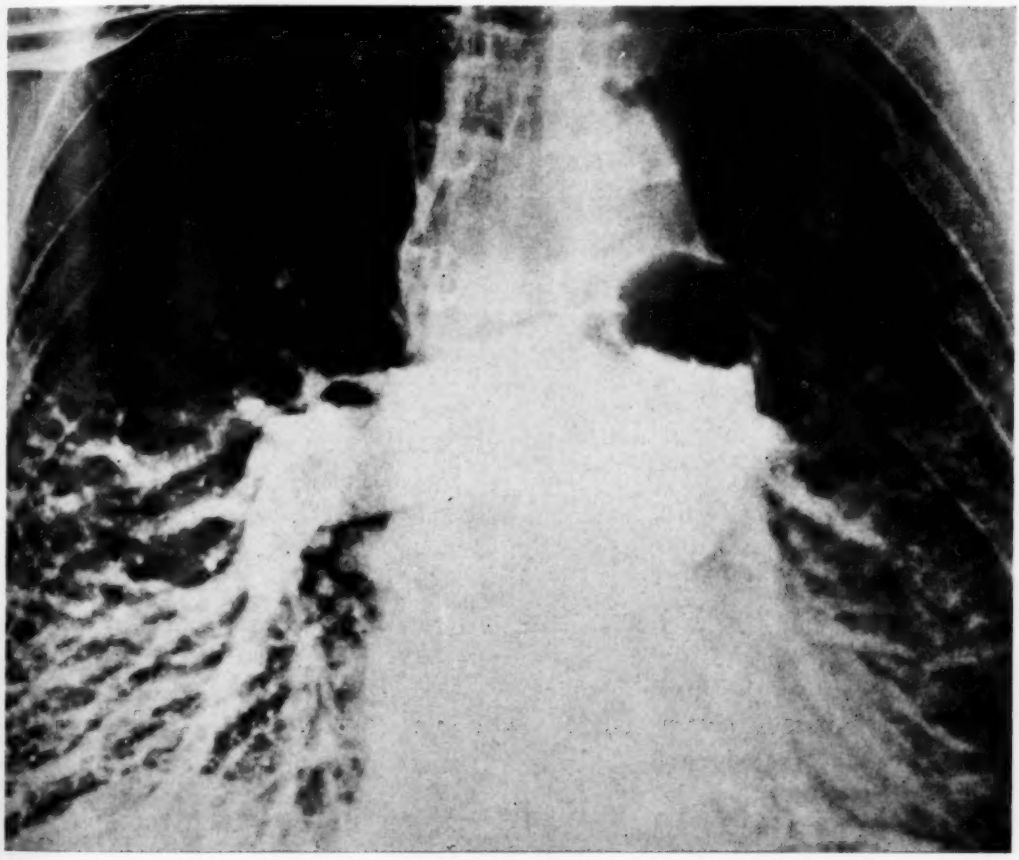

Fig. 1*B*.—Four seconds after injection. Upper third of lung vessels contains air, and lower two thirds contain contrast agent and blood.

CONCLUSIONS

1. Fatal effects of venous air embolism may be prevented by placing the patient on the left side, thereby relieving "air lock" of the right ventricle, permitting venous return to the heart, and distributing most of the gas to the pulmonary arteries of the right lung only.

2. The angiocardiographic appearance of intravascular and intracardiac gas is determined by the patient's position, and so, to an important degree, are the clinical consequences.

Myxedema Ascites: Report of Two Cases

Herbert J. Levine, M.D., and Samuel A. Levine, M.D., Boston, Mass.*

During the past two to three decades, the number of reversible types of heart disease has steadily increased. Among these, heart disease due to disorders of the thyroid gland occupy a prominent place. Hyperfunction of the thyroid gland has been responsible for advanced congestive heart failure and severe angina pectoris, which could be completely abolished by appropriate measures. At first, the effective treatment was a course of iodine followed by subtotal thyroidectomy. Later, thiouracil was introduced and proved to be of value. More recently, radioactive iodine has restored both thyroid activity and cardiac status to normal, and obviated the need for surgery in many instances.

A much rarer cardiac disorder results from decreased thyroid activity, i.e., myxedema heart, which was first described by Zondek.[1] Because of its rarity, it is readily overlooked. This condition can be easily cured, and for this reason, diagnosis is important. The most characteristic feature of this type of heart disease, apart from the customary findings of myxedema, is the increased size of the heart, which produces a silhouette resembling that seen in cases of pericardial effusion. In fact, there is reason to believe that in most cases in which such cardiac enlargement exists, there is considerable pericardial fluid. One wonders whether hydropericardium may not be an invariable finding in cases of untreated myxedema in which there is no other obvious cause for cardiomegaly.

The purpose of this communication is to call attention to the occurrence of ascites as an occasional accompaniment or result of myxedema. This is of some importance because the physician is not likely to think of myxedema when confronted with the problem of ascites, with or without cardiomegaly. In fact, those diseases commonly associated with ascites usually prove to be serious and incurable, whereas the peritoneal effusion of myxedema is totally and easily reversible.

CASE REPORTS

CASE 1.—W. H. was a 60-year-old white man from Venezuela, who entered the Peter Bent Brigham Hospital on June 8, 1958, for evaluation of his cardiac status and ascites. Sixteen years

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Received for publication Feb. 8, 1960.

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prior to admission the patient suffered a myocardial infarction from which he made a good recovery. Thirteen years later he developed symptoms of congestive heart failure which were easily controlled until December, 1956, when he went into frank pulmonary edema. He was treated with digitalis, tourniquets, and diuretics, and remained compensated until 7 months prior to admission. He then developed gaseousness and abdominal distention, and accumulated ascites. He was hospitalized in Caracas, Venezuela, and it was determined that he had cardiomegaly, hepatomegaly, marked ascites, dependent edema, and a normal arterial and venous pressure. Because of a history of moderate alcoholism, a diagnosis of cirrhosis of the liver was entertained. Examination for esophageal varices was negative. He was treated with salt restriction, digitalis, mercurial diuretics, and chlorothiazide. Two paracenteses yielded a total of 11,000 c.c. of ascitic fluid. He continued to do poorly and was transferred to Peter Bent Brigham Hospital, Boston, for further evaluation. There was a strong family history of heart disease on both sides of the patient's family. Past history revealed no known acute rheumatic fever, chorea, hypertension, diabetes, or hepatitis. During the 5 years prior to admission, the patient had taken one grain of thyroid extract daily, but this had been stopped 1 year ago.

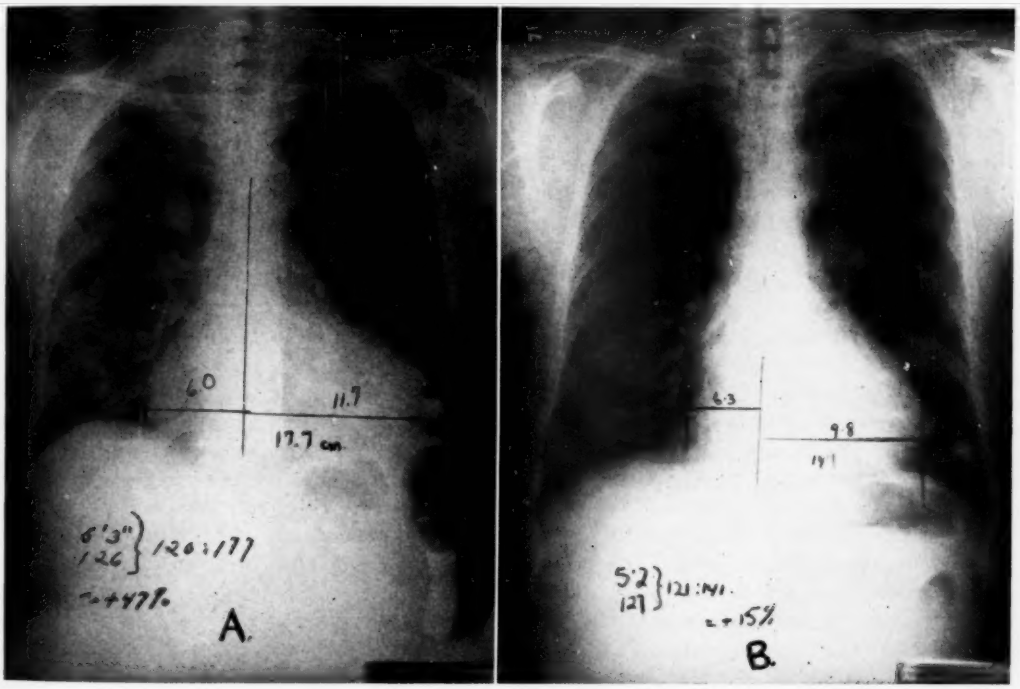

Fig. 1.—Chest roentgenograms of Case 1. *A*, June 20, 1958, before thyroid therapy. *B*, Feb. 16, 1959, after 8 months of thyroid therapy. The transverse cardiac diameter has decreased by 3.6 cm. (17.7 to 14.1 cm.) during this period. Note that the cardiac configuration in the pretreatment film suggests pericardial effusion.

Physical examination revealed a pale, thin man with scant body hair. The blood pressure was 120/80 mm. Hg; pulse, 60; respirations, 20. On funduscopic examination, early arteriosclerotic changes were noted. The tongue was papillated, neck veins were not distended, thyroid was not palpable, and the lungs were clear to percussion and auscultation. The heart was enlarged both to the left and right. All heart sounds were decreased, the first sound more so than the second. No murmurs, gallops, or rubs were heard. The rhythm was regular. The abdomen was protuberant. The liver was felt three fingerbreadths below the right costal margin, and shifting dullness was demonstrable. No other organs or masses were felt. There was one-plus pitting edema of the ankles. Neurological examination revealed slow relaxation of deep tendon reflexes.

Laboratory Data.—Hinton test and urinalysis were negative. Hematocrit varied from 28.5 to 36 per cent. Sedimentation rate was 30 mm./hr.; white blood count was 8,350, with a normal differential; blood urea nitrogen was 17 to 22 mg. per cent. Total protein was 5.5 Gm. per cent; sodium, 132 and 138 mEq./L.; potassium, 6 mEq./L.; carbon dioxide, 29 mEq./L.; chloride, 94 mEq./L.; phosphorus, 1.1 mM./L.; alkaline phosphatase, 2.4 BU; thymol, 6 units; bilirubin, 0.24 mg. per cent; prothrombin time, 90 per cent; Bromsulphalein, 4 and 8 per cent. Venous pressure was 50 and 85 mm. of water; circulation time was 18 and 24 seconds (arm to tongue). The vital capacity was 2.2 and 2.4 liters. Twenty-four-hour radioactive iodine uptake was 5 per cent; red blood cell uptake of radioactive iodine was 10.2 (normal, 11-18). Protein-bound iodine was 0.4μg per cent; basal metabolic rate was −23 per cent. Ascitic fluid from a previous paracentesis had a total protein of 5.0 Gm. per cent, with albumin of 2.1 Gm. per cent and globulin of 2.9 Gm. per cent. The electrocardiogram showed second-degree heart block, left ventricular hypertrophy, sinus arrhythmia, and sinoauricular block. A later tracing showed first-degree A-V heart block (P-R interval of 0.24 second). Chest films and fluoroscopy showed the heart to be enlarged 40 per cent above normal (transverse diameter of heart was 17.8 cm.), with a configuration suggestive of pericardial effusion. Widening of the mediastinum was noted when the patient was placed in the supine position. A small hiatus hernia was seen, but no esophageal varices could be recognized. X-ray films of the skull, barium enema, upper gastrointestinal series, and intravenous pyelogram were all within normal limits, except for questionable pancreatic calcification.

In the hospital, the patient was continued on digitalis and a diuretic regimen. When the diagnosis of myxedema was established, the administration of thyroid extract was begun, 30 and then 60 mg. by mouth daily, but because of the electrocardiographic evidence suggestive of digitalis overdosage, this medication was stopped. The cardiac rhythm became regular, but the P-R interval remained slightly prolonged (0.20 second). He was discharged from the hospital much improved and returned to Caracas. Shortly thereafter, he had another bout of acute left ventricular failure; he was restarted on digitalis and his thyroid dosage was reduced temporarily to 30 mg. daily.

The patient was readmitted to Peter Bent Brigham Hospital on Feb. 15, 1959, 9 months after starting thyroid therapy. In the interim, he had been markedly improved; he was able to walk 3 to 4 kilometers daily and to climb stairs without difficulty, and he had no reaccumulation of either ascites or peripheral edema. On this admission, the color of his skin was better, the blood pressure was 130/80 mm. Hg, and the pulse was 80, with rare extrasystole. Neck veins were flat when the patient was in the recumbent position. Lungs were clear to percussion and auscultation. The heart was somewhat enlarged. The first heart sound was slightly decreased and no murmurs were heard. The liver was felt one to two fingerbreadths below the right costal margin. There was no ascites or pitting edema. The electrocardiogram showed left ventricular hypertrophy, digitalis effect, and a P-R interval of 0.20 second. Chest films and fluoroscopy showed the heart to be 3.6 cm. smaller than on the previous admission, although still 15 per cent larger than normal (Fig. 1). The configuration was that of left ventricular enlargement; there was now no evidence of pericardial effusion. The lung fields were clear, and barium swallow failed to reveal esophageal varices. Venous pressure was 75 mm. of water, and circulation time was 16 second (arm to tongue). Hematocrit was now 39 per cent. Liver function tests were normal, with Bromsulphalein 0 per cent in 45 minutes. Total protein was 7.7 Gm. per cent; albumin, 3.3 Gm. per cent; radioactive iodine uptake was 0 per cent in 24 hours; protein-bound iodine, 2 μg per cent; basal metabolic rate, −13 per cent; serum cholesterol, 275 mg. per cent. A 24-hour urinary F.S.H. excretion was greater than 10 and less than 20 mouse units.

CASE 2.—H. H. was a 63-year-old married white man who was admitted to the West Roxbury Veterans Administration Hospital nine times during the years 1956-1959. When first seen, he complained of nervousness and insomnia and gave a history of hypertension for a period of 20 years. Two years previously he had developed dyspnea, paroxysmal nocturnal dyspnea, loss of weight, and orthopnea, and was found to have atrial fibrillation, mild congestive heart failure, and a blood pressure of 220/120 mm. Hg. He was digitalized and treated with Thiomerin and Diamox, with a loss of weight of 55 pounds. When first seen at the West Roxbury Veterans Administration Hospital, he again was having congestive symptoms with rapid atrial fibrillation

and exhibited marked cardiomegaly. The electrocardiogram showed left ventricular hypertrophy and atrial fibrillation, and a chest film revealed left ventricular enlargement and congested lung fields. The basal metabolic rate was +28 and +32 per cent. Protein-bound iodine was 8.3 and 7.5 μg per cent, and radioactive iodine uptake was 35 per cent. Quinidine caused reversion to normal sinus rhythm, but a regular rhythm was not maintained after he was discharged from the hospital. Because of the question of hyperthyroidism, a suppression test was performed with thyroid extract, but had to be abandoned because of the appearance of severe congestive failure and coronary insufficiency. He was then started on Lugol's solution and propylthiouracil, and experienced marked improvement in his congestive symptoms. Because a drug rash appeared while he was on propylthiouracil, therapy with Tapazole was begun.

In June, 1957, he was again admitted to the hospital, with recurrent congestive heart failure, and was found to have a right pleural effusion and marked cardiomegaly. The liver was felt four fingerbreadths below the right costal margin. There was no ascites. Pitting edema of the legs was present. The electrocardiogram now revealed evidence of a stable anteroseptal myocardial infarction. Radioactive iodine uptake was found to be 40 per cent, and on June 18, 1957, the patient was given 4.28 mc. of radioactive iodine. One week later there was a marked increase in the patient's symptoms, but he responded to a vigorous diuretic regimen.

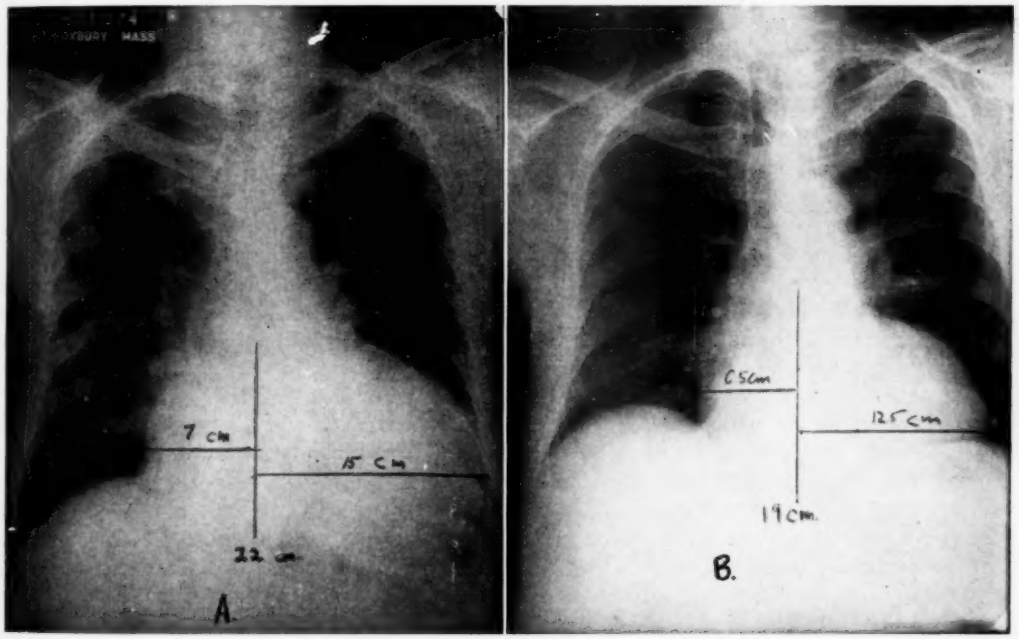

Fig. 2.—Chest roentgenograms of Case 2. *A*, May 7, 1958, before thyroid therapy. *B*, Dec. 4, 1958, after 6 weeks of thyroid therapy. The transverse diameter has decreased by 3.0 cm. (22 to 19 cm.).

During the next 6 months the patient was readmitted to the hospital three times for refractory congestive heart failure. In December, 1957, he exhibited the same cardiomegaly, bilateral basilar râles, and a right pleural effusion. The liver was down four to five fingerbreadths, and there was three-plus pitting edema of the legs. There was no ascites. On that admission there was no albuminuria; bilirubin was 1.9 mg. per cent; alkaline phosphatase, 10.8 units; thymol, 1 unit; Bromsulphalein, 35 per cent. Venous pressure was 340 mm. of saline, and circulation time was 25 seconds (arm to tongue). Radioactive iodine uptake was 34 per cent.

On Dec. 11, 1957, he was given 20 mc. of radioactive iodine and was discharged to return for follow-up. During the next few months the patient improved dramatically; he had an increase in exercise tolerance, and a loss of orthopnea, exertional dyspnea, and peripheral edema. He re-

turned to an active, productive life and stated that his condition was better than it had been for at least 5 years. However, approximately 4 months after the administration of radioactive iodine therapy, and coincident with marked clinical improvement, the patient noted the gradual appearance of abdominal swelling. This progressed and was associated with a gain in weight of 20 pounds. He was readmitted for evaluation in July, October, and December of 1958.

On each of these dates, he was found to be profoundly hypothyroid, with a radioactive iodine uptake of less than 1 per cent and 3 per cent, and a protein-bound iodine of 0.7 and 1.5 μg per cent, respectively. In October, 1958, physical examination revealed a pale, deep-voiced man with dry, coarse skin who was able to lie flat without distress. The blood pressure was 140/90 mm. Hg; pulse was 72 and irregular. Respirations were 16 per minute. Neck veins were flat, and the lungs were clear to percussion and ascultation. The heart was enlarged, with the point of maximal impulse 2 cm. to the left of the mid-clavicular line. The impulse was diffuse. The aortic second sound was greater than the pulmonic second sound; no murmurs, gallops, or rubs were heard. The abdomen was markedly distended and tense. There was shifting dullness and a demonstrable fluid wave. There was a trace of pitting edema of the ankles. Neurological examination gave normal findings, except for slow relaxation of deep tendon reflexes.

Laboratory Data.—Hematocrit was 35 per cent. Sedimentation rate was 33 mm./hr.; white blood count, 5,500, with a normal differential. Urinalysis was normal. Blood urea nitrogen was 22 mg. per cent; fasting blood sugar, 114 mg. per cent; cholesterol, 278 mg. per cent; alkaline phosphatase 5.5 BU; serum bilirubin, 0.32 mg. per cent; thymol turbidity, 1 unit; total protein, 6.8 Gm. per cent, with albumin 4.5 and globulin 2.3 Gm. per cent. Cephalin flocculation was negative; prothrombin time was 100 per cent; Bromsulphalein was 34 per cent (before paracentesis). Electrolytes and the serum electrophoretic pattern were normal. The electrocardiogram now showed atrial fibrillation and right bundle branch block. A chest film revealed cardiomegaly, with prominent left ventricular enlargement and clear lung fields (Fig. 2). Venous pressure was 95 mm. of saline. A cholecystogram was normal.

Five paracenteses were performed over a 6-month period, and yielded from 5 to 12 liters of fluid on each occasion. The ascitic fluid was turbid, slightly greenish in color, and the total protein content varied from 4 to 5 Gm. per cent. On one occasion, the total protein of the ascitic fluid was 4.5 Gm. per cent, with albumin 3.1 Gm. per cent, globulin 1.4 Gm. per cent, and cholesterol 124 mg. per cent. The fluid was repeatedly negative for malignant cells, acid-fast bacilli, and pyogenic organisms. The electrophoretic pattern of the ascitic fluid was grossly similar to that of the patient's serum. A needle biopsy of the liver was performed, and the findings were normal. On Oct. 30, 1958, the patient was started on thyroid extract, 15 mg. by mouth daily; this dose was gradually increased to 45 mg. daily. During the next several months he continued to accumulate ascites, although at a slower rate. Because of the patient's experience with thyroid extract prior to radiothyroidectomy, he was reluctant to increase the dose of thyroid in other than very gradual increments. In February, 1959, following a severe cutback in salary, the patient became extremely depressed, withdrawn, and took to bed. He lost all interest in his surroundings and died quietly at home within a month. An autopsy was not obtained.

DISCUSSION

The first of these two case reports describes a patient who had a myocardial infarction and did well for many years thereafter. He then developed left ventricular failure with pulmonary edema and again recovered. When he was finally seen by us, he had cardiomegaly and ascites, but no orthopnea. It did not appear that he could have ordinary congestive heart failure, despite the cardiomegaly, because the venous pressure was quite normal, and he could lie flat comfortably. The question of tuberculous peritonitis came to mind, but the absence of fever fairly well ruled this out. The possibility of cirrhosis of the liver or abdominal neoplasm was then investigated. The absence of esophageal varices, and the finding of normal liver function tests made the diagnosis of cirrhosis untenable;

and careful x-ray studies of the gastrointestinal tract and negative stool benzidines dismissed neoplasm from consideration. In the course of investigation of the cardiomegaly, thyroid function tests were found to be depressed. Radioactive iodine uptake was 5 per cent, protein-bound iodine 0.4 μg per cent, basal metabolic rate −23 per cent, and it was appreciated that the total protein content of the ascitic fluid was significantly higher than that normally seen in cases of cardiac ascites. At this point, the appearance of the cardiac silhouette was reviewed, and with the clinical impression of myxedema heart in mind, the film was interpreted as being compatible with a diagnosis of pericardial effusion. The partial heart block, which was originally thought to be evidence of heart muscle disease, disappeared when digitalis therapy was stopped. It was considered likely that this arrhythmia was the result of digitalis overdosage. On treatment with thyroid extract, there was a marked decrease in the heart size (Fig. 1) and complete disappearance of ascites. In view of the foregoing data, and particularly because of the excellent state of health which the patient has enjoyed for the past year, it seems quite certain that we were dealing with a case of myxedema ascites.

The second patient had hypertensive heart disease with coronary thrombosis, moderate hyperthyroidism, and severe congestive heart failure. During the period of failure, however, when the venous pressure was markedly elevated (340 mm.), there was no ascites. Radiothyroidectomy produced dramatic improvement in his congestive symptoms. Coincident with the subsequent development of myxedema, and at a time when evidence for congestive failure was entirely lacking, he accumulated massive ascites. At that time, venous pressure was normal, and, except for an elevated Bromsulphalein, the liver function tests and biopsy of the liver revealed no abnormalities.

In both of these cases, the protein content of the ascitic fluid was found to be high—a characteristic of myxedematous effusions which has been noted by others.[2-5] Taipole and Hokkanen[6] found that the total protein of ascitic fluid in eleven cases of cirrhosis was between 0.5 and 2.9 Gm. per cent, with a mean of 1.3 Gm. per cent, whereas in eight cases of congestive heart failure it was between 2.0 and 4.4 Gm. per cent, with a mean of 3.0 Gm. per cent. Myxedematous effusions, however, usually have a protein content of 4.0 to 6.0 Gm. per cent.

Cardiomegaly and ascites are frequent findings in various forms of heart disease. This combination is most commonly met with in rheumatic valvular disease, particularly with involvement of the tricuspid valve or pericardial constriction. In cases of the latter condition, the heart is not likely to be much enlarged, but occasionally, there may be considerable cardiomegaly. In addition, both of these features are seen in cases of the advanced form of almost all kinds of heart disease in which there has been prolonged right-sided heart failure. In all of these conditions, the ascites is either part of the picture of congestive heart failure or is the result of obstruction of the return flow of blood to the heart. In either instance, the venous pressure is, or has been, increased. In those patients with congestion, there would be other evidence of heart failure, such as increased blood volume, a favorable response to digitalis, etc. When ascites and cardio-

megaly occur in patients with myxedema, however, the former does not appear to be a hemodynamic consequence of heart failure, but rather an apparently independent effusion.

Serous effusions in cases of myxedema are not uncommon. Although the early instances of proved pericardial effusion in cases of myxedema were reported by Gordon[7,8] in 1929, the suggestion that pericardial effusion was a " 'constant' early and major factor in the cardiac syndrome of hypothyroidism" was not made until 1949.[5] With the appearance of additional cases in the literature supporting this view, it is now generally believed that this phenomenon accounts for most of the large hearts seen in patients with untreated myxedema.

Ascites, on the other hand, is decidedly less common. Fournier reported five cases of myxedema ascites and quoted Nothnagel as having seen another.[8] Marsh removed 5 gallons of peritoneal fluid from one patient with myxedema who subsequently underwent exploratory laparotomy. All abdominal organs were found to be grossly normal, and with thyroid medication, ascites disappeared.[9] Evans reported an unusual case of myxedema ascites with bladder atony—the latter viscus contained 2,500 c.c. of urine. He also was one of the first to note the high total protein content of the myxedematous ascitic fluid.[2] Other cases have been reported of multiple serous effusions in myxedema which regressed promptly on treatment with thyroid.[10-13]

The pathogenesis and physiologic significance of effusions in cases of myxedema remain unclear. Recent hemodynamic studies by Graettinger and associates[14] have shown that patients with myxedema, with or without pericardial effusions, have a low resting cardiac output which, unlike that of patients in congestive failure, increases normally with exercise and is associated with a normal decrease in peripheral vascular resistance. Arterial venous oxygen differences were normal in all but a few instances. The catheterization findings, furthermore, revealed normal or only slightly elevated right atrial pressure in most of these patients. These findings, plus many clinical observations, demonstrate that the pericardial effusion of myxedema per se does not embarrass cardiac function significantly, nor does it produce signs of right heart failure. Thus, as in the two cases reported in this paper, one cannot necessarily attribute ascites to heart failure, especially when the venous pressure is normal. Indeed, the presence of true congestive failure in patients with myxedema is not common, and is usually associated with ancillary coronary artery or valvular heart disease. In rare instances, true congestive heart failure is found in patients with myxedema when there is no other apparent cause.[13,15] In such cases, cardiac dilatation, with little or no pericardial fluid, has been found.

Why one person with myxedema develops ascites, and another does not, remains a mystery. Of possible significance is the observation that both of the patients reported upon in this paper had right-sided failure at a previous time, although at the time that the ascites appeared, the venous pressure was entirely normal. Possibly, the remote stress imposed upon the liver rendered this organ more susceptible to the biochemical changes of subsequent hypothyroidism.

SUMMARY

Two cases of myxedema ascites are reported. Both patients had had previous congestive heart failure, but at the time of appearance of the ascites, they were found to have normal venous pressures, normal liver function tests, ascitic fluid with a high total protein content, cardiac silhouettes suggestive of pericardial effusion, and definite hypothyroidism. In both instances, a careful search was made for cardiac and intra-abdominal causes of ascites, and none could be found. One patient experienced dramatic improvement in his general condition and complete disappearance of his ascites on thyroid medication. The second exhibited a decrease in the accumulation of peritoneal fluid, but died before optimal therapy had been attained. A needle biopsy of the liver in the second patient revealed no abnormalities. The pathogenesis of ascites in cases of myxedema remains unclear, but does not appear to be related to the hemodynamic consequences of pericardial effusion and/or elevation of the venous pressure. It is evident from clinical and hemodynamic studies of the so-called "myxedema heart," that even when free fluid is present in the pericardial, pleural, or peritoneal spaces, congestive heart failure, as it is customarily understood, rarely exists. Myxedema ascites, although rare, is easily and totally reversible with appropriate thyroid therapy.

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Clinical-Pathologic Conference

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CLINICAL ABSTRACT*

A 14-year-old Negro boy was admitted to LaRabida Jackson Park Sanatarium for the last time on July 4, 1958, with complaints of chest pain, cough, and dyspnea.

Initial Hospitalization (July 1, 1949 to Sept. 22, 1949).—

History: The patient was born in 1943, after a normal full-term pregnancy. No abnormalities were noted at birth. He developed satisfactorily and received the usual immunizations. He had measles at age 1½ years. Symptoms of his illness first appeared at the age of 6 years. Sore throat accompanied by anorexia and vomiting was followed by respiratory difficulty, lethargy, and abdominal pain, and he was admitted to another hospital on July 1, 1949. His sister, then 7 years of age, had been hospitalized with "rheumatic fever" a few months earlier. Although the family's living conditions were extremely crowded, there was no other known disease contact.

Physical examination: The child's face was puffy, and his tonsils were reddened and enlarged. Generalized shotty lymphadenopathy was noted. Blood pressure was 104/74 mm. Hg. Pulse rate was 150 per minute, and femoral pulses were palpable. Temperature was 99.2° F. Breathing was labored and rapid. Wheezing breath sounds and an apical systolic murmur were heard on auscultation. A tender liver extended 5 fingerbreadths below the right costal margin. The spleen could not be palpated.

Laboratory examination: Hemoglobin was 11.5 Gm. per cent; white blood cell count was 12,300/mm.^{3} with 62 per cent neutrophils, including 15 per cent band forms on the peripheral smear. Erythrocyte sedimentation rate was 9 mm. per hour. A sickling preparation was negative. Serum nonprotein nitrogen, phosphorus, alkaline phosphatase, icterus index, thymol turbidity, and cephalin flocculation values were within normal limits. Urinalysis was negative. Mantoux test, 1:10,000, was negative.

Hospital course: His condition improved gradually on bed rest, penicillin, and aspirin. One month after admission the apical impulse was palpable outside the left mid-clavicular line in the sixth intercostal space, and a systolic thrill was palpable over the apex. A loud, harsh, systolic murmur was heard over the entire precordium, maximally at the apex and transmitted to the axilla. The pulmonic second sound was accentuated.

He was discharged on Sept. 22, 1949, with his lungs clear to auscultation and his liver decreased in size. He was hospitalized again a few days later in respiratory distress. He had developed two-pillow orthopnea, epigastric pain, nausea, and pain in both knees and ankles. His tonsils

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From the LaRabida Jackson Park Sanatarium, and the Departments of Medicine and Pathology of the University of Chicago Clinics, University of Chicago, Chicago, Ill.

The Conference was organized under the direction of Dr. Robert W. Wissler and Dr. Seymour Glagov.

Received for publication Jan. 5, 1960.

*Part of the clinical history was obtained from the medical records of the Cook County Hospital and the Presbyterian-St. Luke's Hospital, Chicago, Ill.

were again injected. The extremities showed no abnormalities. Treatment with penicillin, aspirin, oxygen, digitalis, and mercurials resulted in some improvement. He was transferred to LaRabida Jackson Park Sanatarium for further study on Nov. 15, 1949.

During the next 8 months at LaRabida Sanatarium (Nov. 15, 1949 to July 27, 1950) he was treated with penicillin and sulfadiazine for long periods. Venous pressure was 100 mm. H_2O. Laboratory values were essentially unchanged; erythrocyte sedimentation rates varied between 3 and 11 mm. per hour; repeated sickle cell preparations were negative.

Throat cultures were repeatedly negative for beta hemolytic streptococci. There was an episode of severe exudative tonsillitis, with subsequent suppuration of a cervical lymph node. A smear of pus from the node was negative for acid-fast bacilli, and guinea pig inoculation and culture were negative. A tuberculin patch test was positive. Repeat subsequent auscultations of the heart revealed a low-pitched, harsh, systolic murmur which was heard best at the apex, a loud pulmonic second sound and a mid-diastolic apical murmur. The thrill was no longer palpable. By the time of his discharge on July 27, he had progressed to full activity, and digitoxin was discontinued.

X-ray examination (Dr. Williams): The initial x-ray examination at LaRabida on Nov. 15, 1949, included a frontal chest film (Fig. 1), left anterior oblique film (Fig. 2), and right anterior oblique film (Fig. 3). The pulmonary vasculature was normal; it was neither increased nor decreased, so that there was no indication of either left-to-right or right-to-left shunt. The main pulmonary artery was normal in size. The aortic arch was small; the position of the ascending aorta was not visible. The right anterior oblique film (Fig. 3) showed posterior displacement of the esophagus by an enlarged left atrium, but the displacement extended all the way to the diaphragm, thus indicating that there was considerable ventricular enlargement as well. The radiographic differentiation between right and left ventricular enlargement is extremely unreliable since the interventricular groove is rarely visible. Electrocardiography is a much more reliable way of determining ventricular predominance than is x-ray examination.

Electrocardiographic examination (Dr. Jones): The electrocardiogram of Nov. 16, 1949 (Fig. 5,*a*), showed left axis deviation with S-T depression and a low diphasic T wave in Lead I. The P wave was abnormal and appeared to be inverted in Leads II and III, suggesting a nodal origin. However, the P-R interval was 0.12 second, which would not be abnormally short for this child's age.

The tracing made on Dec. 19, 1949 (Fig. 5,*b*), showed an increasing amplitude of QRS and a tremendous increase in the height of P waves in Leads II and III.

Clinical course (continued): From 1950 to 1958, the patient attended school. His physical activity was limited to slight exertion. He was seen regularly at another clinic and treated with sulfadiazine and penicillin. Tonsillectomy was performed during this period. The cardiac enlargement, prominent systolic apical murmur, and loud second pulmonic sound were repeatedly noted.

During the first 6 months of 1958, he was hospitalized three times at another hospital. The first hospitalization, for a week in January, followed a day of precordial and substernal pain. His liver was slightly enlarged and tender, but all symptoms disappeared after a week of bed rest and aspirin. The second admission, from May 1 to 27, followed week-long symptoms of a "cold" with a cough productive of blood-streaked sputum. Nocturia (1x), orthopnea, and exertional dyspnea were present, but no fever, chills, or malaise. His nail beds were dark; his liver was enlarged. Neck veins were distended and hepatojugular reflux was present. Wheezes were heard in his chest. He improved with digitalization. His pulse rate fell from 100 to 80 per minute, and the venous distention and hepatojugular reflux disappeared rapidly. The third admission, in June 1958, followed complaints of respiratory difficulty. Moist râles and wheezes were audible in both lung bases. The expiratory phase was prolonged. The use of gitalin, diuretics, and bronchodilators resulted in a rapid loss of weight and disappearance of his venous distention. However, respiratory symptoms were more resistant to therapy. Bronchoscopy performed on June 17, 1958, revealed "chronic bronchitis with thick secretions in both main bronchi."

Cardiovascular physical findings were comparable during these three admissions. The heart was enlarged, with a strong maximum impulse in the sixth intercostal space in the left anterior axillary line. There was a left parasternal lift. The very loud pulmonic second sound in the left second or third intercostal space was not split. An apical systolic thrill was present; a loud harsh

precordial systolic murmur was maximal at the apex and transmitted to the axilla; an occasional systolic murmur at the base radiated to both sides of the neck; an apical mid-diastolic or presystolic murmur was heard.

Pulmonary function studies showed a diminished vital capacity (35 per cent of predicted) and maximal breathing capacity (26 per cent of predicted), whereas oxygen saturation by ear oximetry was 82 per cent. Several days later the vital capacity was 57 per cent and the maximal breathing capacity was 47 per cent, with no significant improvement after Isuprel. Oxygen saturation by ear oximetry was 92 per cent and rose to a maximum of 96 per cent during the breathing of oxygen for 6 minutes.

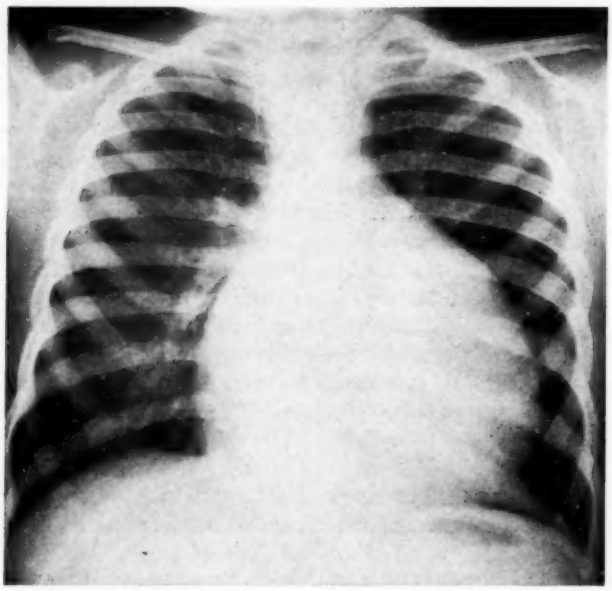

Fig. 1.—Frontal chest film taken on Nov. 15, 1949.

Right heart catheterization was performed and was "complicated by the presence of marked ventricular irritability which precluded catheterization of the pulmonary artery." Pressures at rest were: superior vena cava, 9 mm. Hg (mean); right atrium, 6 mm. Hg (mean); right ventricle, 45/7 mm. Hg; peripheral artery, 90/68 mm. Hg. Pressures after exercise were: right atrium, 5 mm. Hg (mean); peripheral artery, 98/65 mm. Hg. Oxygen saturation in blood samples at rest was: innominate vein, 49 per cent; superior vena cava, 48 per cent; right atrium, 47 per cent; and peripheral artery, 94 per cent. After exercise the oxygen saturation was: right atrium, 40 per cent, and peripheral artery, 92 per cent. At rest, the heart rate was 111 per minute; cardiac output was 1.78 L. per minute; cardiac index was 1.19 L./min./M.^{2}; and stroke volume index was 11 c.c./beat/M.^{2}. After exercise the heart rate was 120 per minute; cardiac output was 1.94 L. per minute; cardiac index was 1.29 L./min./M.^{2}; and stroke volume index was 11 c.c./beat/M.^{2}. On deep breathing, the right atrial pressure tracing showed increased V waves.

Laboratory examination: Eleven blood cultures during this period were negative. Hemograms and erythrocyte sedimentation rates were unchanged from previous values.

Final Hospitalization (July 5, 1958 to Oct. 24, 1958).—The final admission followed an episode of respiratory difficulty.

Physical examination: The pulse rate was 120 per minute. Respiratory rate was 30 per minute. Blood pressure was 112/90 mm. Hg. The cardiac point of maximum impulse was in the left anterior axillary line at the level of the fifth intercostal space. The apical systolic thrill and murmur were present, as was a Grade 2 diastolic murmur. The liver was enlarged. The lungs were clear.

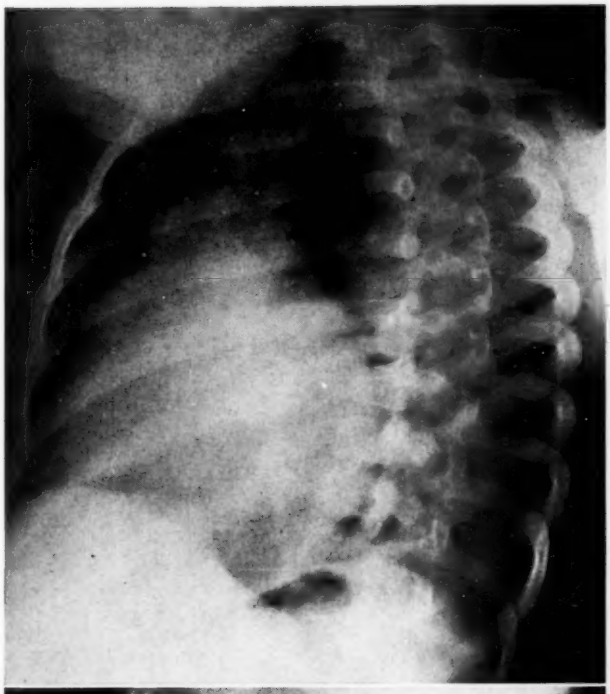

Fig. 2

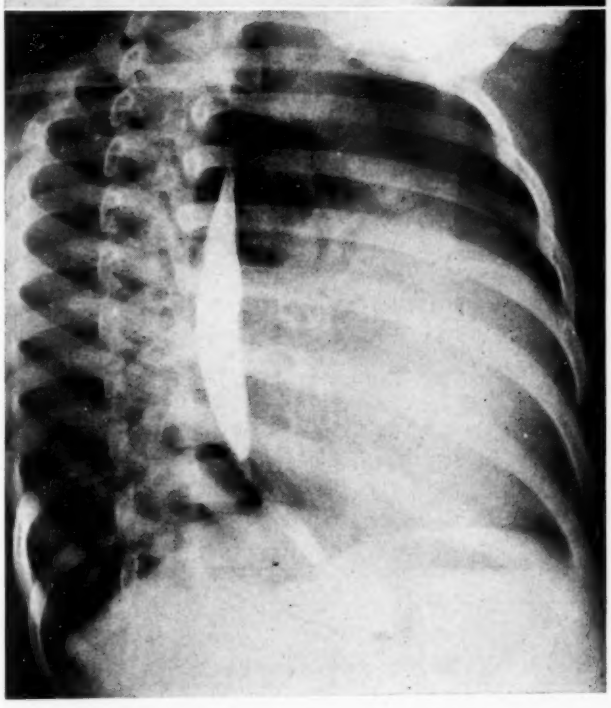

Fig. 3.

Fig. 2.—Left anterior oblique chest film taken on Nov. 15, 1949.
Fig. 3.—Right anterior oblique chest film taken on Nov. 15, 1949.

Laboratory examination: Hemoglobin values ranged between 10 and 13.6 Gm. per cent. Initially, the white blood cell count was 11,200/mm.^{3}, and the sedimentation rate was 11 mm. per hour. The white blood cell count subsequently fell to normal values, but the erythrocyte sedimentation rate rose to 31 mm. per hour terminally. Urinalyses consistently showed 3+ albumin. During October, serum electrolyte determinations showed: serum sodium, 120 mEq./L.; chloride, 89 mM./L.; and carbon dioxide, 30.6 mM./L. Previous values had been normal. Two determinations of anti-streptolysin-O titer were 300 and 100, respectively, and C-reactive protein test was 2+.

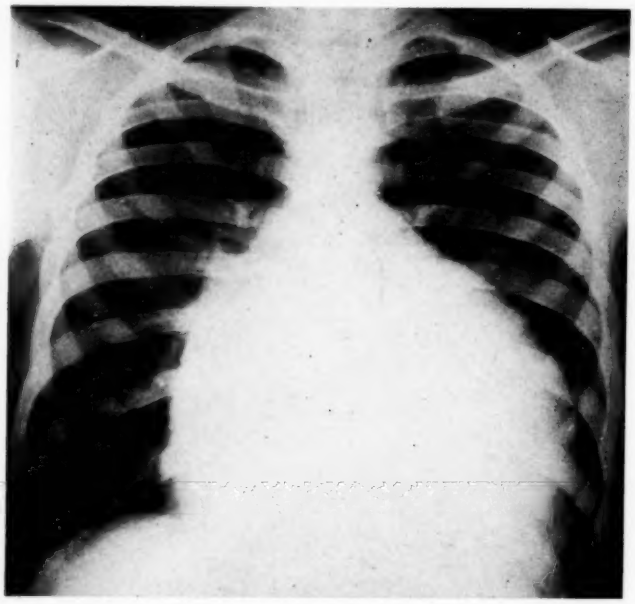

Fig. 4.—Frontal chest film taken on July 7, 1958.

Hospital course: Atrial fibrillation supervened. Although the patient's lungs were at first clear, right-sided dullness and decreased breath sounds appeared. The liver remained enlarged. During the last 3 weeks of his life he complained of abdominal pain, vomited, and coughed up blood-tinged sputum. Asthmatiform breathing became resistant to bronchodilators. On October 24, he was found gasping and no heartbeat could be heard. Breathing soon ceased.

X-ray examination (Dr. Williams): The x-ray film (Fig. 4) taken on the last admission in July, 1958, showed a marked increase in heart size, with a double contour on the right heart border from an enlarged left atrium. There was no pulmonary edema. The film taken in September, 1958, showed an area of pneumonia in the right upper lobe; this had cleared by October, 1958.

Electrocardiographic examination (Dr. Jones): The electrocardiogram recorded on Oct. 3, 1958 (Fig. 5,*c*), showed a great increase in the amplitude of P waves in Leads II and III, which blended with the QRS complexes because of the relatively short P-R intervals. R_I and S_{III} had increased greatly in amplitude and slurring, which suggested increasing left ventricular hypertrophy. S-T segments and T waves were obscured by the large auricular T waves.

The tracing made on Oct. 6, 1958 (Fig. 5,*d*), showed giant P waves in Leads II and III, and a broadly notched P_I. The P-R interval was now prolonged as in first-degree heart block. The marked left ventricular hypertrophy persisted, now with S-T depression in Lead I and S-T elevation in Leads II and III.

The final tracing (Fig. 5,*e* recorded on Oct. 23, 1958) showed the appearance of auricular fibrillation with occasional premature ventricular contractions. The QRS amplitude had become much reduced, and S-T deviations were less pronounced than in the earlier tracings. T waves remained low and diphasic.

DISCUSSION

DR. JONES: Symptoms first appeared at the age of 6 years, when the patient was hospitalized after an acute illness which lasted 5 days and consisted of a sore throat, anorexia, and vomiting, and which was followed by respiratory difficulty. Apparently his temperature was normal. Wheezing breath sounds, cardiomegaly, an apical systolic murmur, and a large tender liver all point to congestive heart failure. Of particular interest is the fact that the erythrocyte sedimentation rate was only 9 mm. per hour.

The examination made 1 month after admission gives us some additional information: the point of maximum impulse was palpable outside the left midclavicular line in the sixth intercostal space, a systolic thrill was palpable over the apex, the pulmonic second sound was accentuated, and a loud, harsh systolic murmur was heard over the entire precordium, maximally at the apex and transmitted to the axilla. This certainly sounds like the apical murmur of mitral insufficiency.

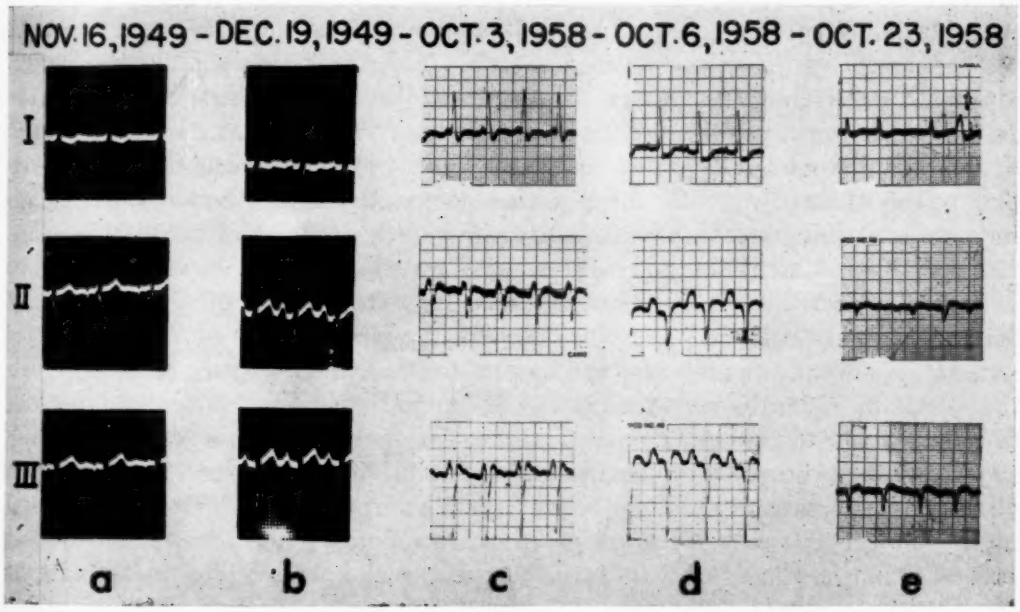

Fig. 5.—Electrocardiographic studies during successive hospitalizations.

Shortly after his discharge he was hospitalized again for respiratory distress. Although he was said to have had pain in both knees and ankles and his tonsils were again injected, his extremities were not remarkable. In other words, there was no objective evidence of arthritis, and at no other time is this symptom mentioned. After he was transferred to LaRabida Sanatorium, the chief abnormality of his vital signs was the increased respiratory rate. Auscultation of the heart again revealed a low-pitched, harsh, systolic murmur which was heard best at the apex, and a loud pulmonic second sound. This time mention is made of a mid-diastolic apical murmur. No thrill was discovered at first, although at later examinations

a thrill is mentioned. There was a posterior bulging of the esophagus, which would suggest perhaps some left auricular enlargement. The electrocardiogram showed tachycardia, suggested a nodal rhythm, with perhaps some prolongation of A-V conduction in view of the normal P-R interval (Fig. 5,*a*), and showed left ventricular hypertrophy. The sedimentation rate was generally between 3 and 11 mm. per hour. At the time of discharge he had progressed to full activity.

He was followed up for about 8 years, in the Clinic. During this time he was able to attend school, although physical activity was limited. During the first 6 months of 1958, he was hospitalized three times, one time for what appears to have been an attack of pleurisy, although his liver was found to be enlarged and tender at this time. The second hospitalization, a few weeks later, was for a cough with blood-streaked sputum and vomiting. There was also nocturia, orthopnea, and exertional dyspnea, but I would emphasize again that there was no fever, chills, or malaise. The neck veins were distended, the nail beds were dark, the liver was enlarged, and the hepatojugular reflux was positive. Although edema was absent, this child undoubtedly had right heart failure. On the other hand, his vital capacity and his breathing capacity were strikingly reduced. Arterial oximetry was repeated several times and was found to vary from 92 to 96 per cent (after breathing oxygen); this is certainly not sufficiently low to establish any right-to-left intracardiac shunt. Right heart catheterization revealed that there was no shunting of arterialized blood into the right heart, at least as proximal as the right ventricle. We do not know about the pulmonary artery, but there is no clinical suggestion here of a patent ductus. The cardiac index was strikingly low. On deep breathing, the right atrial pressure tracing exhibited some increase in the height of the V waves; if this were a regular finding, we might consider a tricuspid insufficiency. However, this is presented as being somewhat equivocal.

He was finally readmitted to LaRabida Sanatarium in July of 1958. Until mid-October, 1958, there was not much change in the physical findings. The chief findings remained: cough, dyspnea, and occasional increase in the size of the liver. There were several bouts of arrhythmia, and at one time it was thought that he had a pneumonitis on the basis of x-ray evidence. Electrolytes showed a dilution hyponatremia with low sodium, low chlorides, and some alkalosis, but this was transient and not characteristic of the entire period. The determinations of antistreptolysin-O titer were 300 and 100, respectively, and the C-reactive protein was 2+. During the last 2 weeks of his life he complained of abdominal pain, vomiting, and cough productive of blood-tinged sputum. Asthmatiform breathing became resistant to bronchodilators. On Oct. 24, 1958, he was found gasping, no heartbeat could be heard, and breathing ceased several minutes later. A sudden exitus indeed!

Here we have a 14-year-old boy who had two periods of illness, one at the age of 6 years and the second during his fourteenth year. The attending staff presumed that his illness was due to acute and chronic rheumatic myocarditis, for the following reasons: (1) There was evidence of cardiomegaly and congestive failure in a child. (2) Murmurs were described which were quite characteristic of mitral insufficiency, and later a diastolic murmur at the apex suggested be-

ginning stenosis. (3) There was delayed atrioventricular conduction, as shown by the lengthened P-R interval; there were many changes in the P waves, and auricular fibrillation was documented twice. (4) The electrocardiogram showed good evidence for left ventricular hypertrophy. (5) Catheterization showed no convincing evidence of arterial unsaturation, and there was a modest pulmonary hypertension which might go along with his congestive failure. In addition, he had recurrent attacks of tonsillitis. The electrocardiograms, taken during this hospitalization (Fig. 5,*c*), presented P waves which were even larger than previously, at first with a short and then with a prolonged P-R interval, and a left ventricular hypertrophy pattern with an increased S-T depression, perhaps the result of digitalis effect. The last tracing documents another recurrence of atrial fibrillation, but with a lessening of the total QRS amplitude, which suggests a more advanced myocardial deterioration. From the electrocardiograms we may conclude that this boy had left ventricular and right atrial hypertrophy with episodes of nodal and atrial arrhythmia, and possibly myocarditis.

Now there are certain inconsistencies in the diagnosis of rheumatic heart disease. In the first place, there is no history of rheumatism or chorea. Fever was not a prominent symptom and was, in fact, absent except for a few days when other intercurrent infections were demonstrable. Cough and dyspnea were the prominent symptoms; the former was so prominent that the patient was subjected to bronchoscopy at one time. The sedimentation rates and C-reactive protein were seldom elevated. Antistreptolysin-O titer was elevated above 1:250 on only one occasion and was otherwise below 1:250. This is rather remarkable in view of the fact that he had such frequent attacks of tonsillitis.

We see from the x-ray films why there was some difficulty in deciding between left and right ventricular hypertrophy on the basis of x-ray examination, but certainly the electrocardiograms left little doubt that there was marked left ventricular hypertrophy. The question as to whether the right or left atrium was enlarged is hard to answer by x-ray examination in such a case of gross cardiac enlargement. The one thing we can cling to here is that the patient did have a small aortic knob, and a second perhaps is that there was no unusual hilar vascularity. The latter was not increased as we might expect in patients with congestive failure.

The small aortic knob suggests certain possibilities. Coarctation of the aorta comes to mind, but there is no hypertension here, and by this age, one might expect some rib notching. The electrocardiographic evidence of left ventricular hypertrophy would be compatible, but the femoral pulse was palpable and this fairly well dismisses that diagnosis. The small aortic knob also suggests some congenital anomaly of the aortic arch. These can be associated with frequent respiratory infections, but careful fluoroscopy would have revealed such an abnormality. Furthermore, such pulmonary infections as are usually produced by these abnormalities would probably show up much more obviously than we have seen here on either physical or chest x-ray examination. These anomalies by themselves are not likely to produce congestive heart failure or the murmurs that were heard. Hence, if this is the explanation for the small aortic knob, the patient must also have had rheumatic heart disease.

Another congenital anomaly which sometimes masquerades as rheumatic heart disease is Ebstein's anomaly. This is characterized by displacement of the tricuspid valve downward in the right ventricle and may produce right atrial hypertrophy. However, a patient with this condition is usually cyanotic. Cyanosis might have been masked in a Negro child, but the oximetry studies provided good evidence that there was no arterial unsaturation. Also, this condition usually produces a right bundle branch block, with evidence of left ventricular hypertrophy on the electrocardiogram, and this is not seen here.

I believe that we are dealing with a condition that falls into the group of "congenital idiopathic hypertrophies" of the heart. These conditions include endocardial fibroelastosis, glycogen storage disease of the heart, rhabdomyoma, interstitial myocarditis, beriberi heart disease, and anomalous coronary arteries. Because of the prominence of murmurs in this case the most likely possibility is endocardial fibroelastosis. This is a very pleomorphic condition and one of the most frequent of congenital abnormalities. It may occur at almost any age of life, although it is much more frequent in infants, and is said to be the most common cause of death due to heart disease which occurs under the age of 2 years. These patients do not ordinarily have right ventricular hypertrophy but characteristically present a left ventricular hypertrophy pattern on the electrocardiogram. They have large P waves, and atrial electrocardiographic abnormalities which often presage arrhythmias. This disease involves the endocardium, often irregularly, sometimes on only one side of the heart. It also involves one or more of the valves, and the involved valves may be more or less stenotic or insufficient. The mitral, tricuspid, and aortic valves may be involved. Other developmental anomalies, such as coarctation of the aorta or hypoplastic aorta with bicuspid aortic valve, are often associated. There may or may not be cyanosis, but when it does occur, it is frequently intermittent. Cardiac catheterization would reveal no shunt except in the event of an incidentally associated septal defect. This would also be compatible with the general reduction in cardiac output which we see so dramatically here. Actually, the only objection I can see to this diagnosis is the patient's age and rather chronic course. Eighty per cent of the infants with this disease die before 1 year of age, and it has been said that 95 per cent or more die before the age of 3 years. More important, in most cases the illness lasts only a few weeks after the onset of symptoms, although in other cases, remissions and exacerbations extend over a few months to a year. I have not been able to find another case with a 10-year history of symptoms such as this patient presents, but the initial symptoms may have been provoked by an acute infection, with his terminal heart failure lasting only about 10 months. My final diagnosis then is: *Congenital heart disease, probably endocardial fibroelastosis with a hypoplastic aorta and perhaps a bicuspid aortic valve, with mitral insufficiency and possible aortic stenosis.* In any case, there should be left ventricular hypertrophy and a large right auricle.

DR. GROSSMAN: Dr. Jones mentioned certain inconsistencies in the diagnosis of rheumatic fever and rheumatic heart disease in this patient and noted the absence of rheumatism and chorea. In children, especially those who develop rheumatic fever early, the absence of polyarthritis and chorea is not uncommon,

and these children may present with only signs of carditis, with or without failure. The absence of fever by the time the child is seen by the physician is not unusual.

As Dr. Jones has pointed out, the fact that the erythrocyte sedimentation rate was only 9 mm. per hour is unusual in the early acute stages of rheumatic fever. Of course, in the presence of cardiac failure this finding too may be noted.

DR. JONES: The point I wish to make is that during many months and even years of rather close observation this boy showed no clinical or laboratory evidence of rheumatic fever if we exclude the cardiac findings.

DR. CASSELS: It seems to me, however, that the pulmonary vasculature is less than you might expect to find in relation to the size of the heart. Perhaps this discrepancy is more noticeable because the heart is very large. As Dr. Jones points out, it just does not seem to be the picture of pulmonary congestion. As a matter of fact, there is a question whether the pulmonary flow not only is not increased but perhaps reduced. Dr. Jones mentioned another aspect of the x-ray picture that seems important, namely, that compared to the size of the heart the aorta is small. And you know that if the upper mediastinum lies predominantly to the right of the midline, a right aortic arch must be considered. In these x-ray films, the right upper mediastinum appears quite vacant. The aorta is clearly on the left, and I think that the border of the descending aorta can be seen. Because of the absence of the usual shadow of the ascending aorta it must be concluded that the aorta either (1) is markedly diminished in size or (2) does not lie in its usual position. Smallness occurs with a great reduction in left ventricular output, as in the case of atrial septal defects, wherein hypoplasia of the aorta can be quite marked, or the aorta can be hypoplastic because of stenosis, or I suppose that there can be congenital smallness of the aorta. If it is displaced, it ought to be displaced to the opposite side or to the left. I suppose that it could also be in the midline and anterior and not be readily visible. This raises the question of some kind of transposition. It is true that he was mildly cyanotic at the time.

On the x-ray film (Fig. 1) there is a peculiar bulge that lies at about the position of an enlargement or hypertrophy of the right ventricular outflow tract secondary to pulmonary stenosis. Since the ascending aorta does not appear in its usual position, does the aorta originate on the left, and is the apparent large pulmonary artery really the ascending aorta?

Cardiac catheterization led to a diagnosis of mitral disease. If the pulmonary artery is entered during cardiac catheterization, the relative position of the pulmonary artery and the aorta can usually be identified. If the pulmonary artery is medial and the aorta lateral, this is corrected transposition; and this general diagnosis is very helpful clinically. Although the abnormal position of the vessels themselves do not cause abnormal hemodynamics, other congenital defects are usually associated and these are frequently severe. Although the aorta arises from the physiologic left ventricle, anatomically this is the right ventricle, and abnormalities of the tricuspid valve, which lies in the usual position of the mitral valve, sometimes occur. I have seen such a deformity similar to Ebstein's mal-

formation on the aortic ventricle, and the clinical picture is that of mitral regurgitation. This possible diagnosis is based on the absence of the ascending aorta in the usual place. Even though there is not sufficient information to establish this diagnosis, it must be considered in the differential diagnosis.

DR. JONES: Well, I considered pulmonic stenosis because of the elevated systolic pressure on catheterization, but it seemed to me that there should be more evidence on physical examination if this were an isolated pulmonic stenosis, and I was willing to accept the fact that there was no demonstrable shunt in the heart. As far as corrected transposition is concerned, my impression was that this should have been recognized by fluoroscopic examination. Since no mention is made of an increased breadth of the mediastinum on the oblique view, I did not consider this a serious possibility. In view of the associated defects you mention, I should think that there should have been more evidence for cyanosis than there was in this boy, at least in the lower extremities.

Fig. 6.—Heart in situ, anterior view after removal of sternum. The aorta and pulmonary trunk arise at approximately the same anteroposterior level, the aorta on the left and the pulmonary trunk on the right. The two vessels course parallel to each other.

DR. CASSELS: Well, if there was no shunt, it would not require this. If there is no septal defect, cyanosis is not necessary. I think that I have built a structure on a very small foundation.

DR. GRANSTON: At the time of autopsy this boy weighed 41.8 kilograms, and measured 159 cm. in length. Peripheral edema was not demonstrable. There were 360 c.c. of fluid in the pericardial sac. It was immediately apparent that a congenital anomaly of the heart and great vessels was present. Instead of the

normal relationship between the pulmonary trunk and aorta, the two vessels arose at approximately the same anteroposterior level and coursed parallel to each other (Fig. 6). This was not quite the configuration of a complete transposition, for the vessel arising from the left side of the heart supplied the systemic circulation. The pulmonary trunk was slightly larger than the aorta, but the aorta was not hypoplastic. The aortic arch, instead of arching from the right to the left as normally, actually passed directly posteriorly, if not slightly to the right, but did pass to the left of the trachea and esophagus. The persistent clinical finding of the loud second "pulmonic" sound in the second left intercostal space was probably related to the aortic valve, because the base of the aorta arose to the left of the pulmonary trunk rather than posterior and slightly to the right as is seen normally.

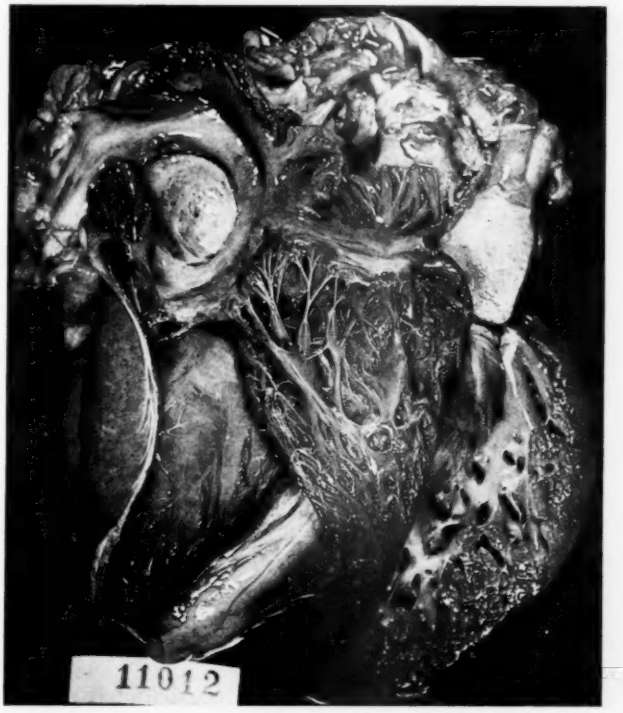

Fig. 7.—Opened heart, exposing right atrium, right-sided atrioventricular (mitral) valve, and right-sided (morphologic left) ventricle. Part of the coronary venous return emerges from between the pectinate muscles of the auricle above the anterior leaflet of the valve.

The heart was greatly enlarged: it extended to the left lateral thoracic wall. It weighed 560 grams, probably twice the normal size for this age. The anterior interventricular groove and the apex pointed to the left. The ventricle on the left side was so tremendously enlarged that the posterior interventricular groove was displaced to the right lateral margin. There was a fine roughening of the epicardial surface over the left atrium and the origins of the great vessels.

I will describe the chambers of the heart by following the course of the blood. The right atrium was dilated and somewhat hypertrophied. On its septal wall

there was a fossa ovalis with a limbus. The foramen ovale was obliquely patent to the probe but should have been competent in the absence of an increase in right atrial pressure above that of the left atrium. On the right side the atrioventricular valve had two well-formed cusps, and resembled a bicuspid or mitral valve (Fig. 7). The ventricle on the right side was dilated and moderately hypertrophied. However, the architecture of this ventricle was rather that of a left ventricle. There was no crista supraventricularis dividing this ventricle into a conus portion and a sinus portion. The posterior leaflet of the atrioventricular valve was continuous with the pulmonic semilunar valve in much the same way as the anterior mitral leaflet is continuous with the aortic valve in a normal heart. The membranous septum was visible beneath the pulmonic valve. In addition, the septal wall of this ventricle was smooth, with no chordae tendineae arising from the septal wall. Compared to a normal *left* ventricle the ventricular wall would be considered atrophic, but compared to a normal right ventricle it was hypertrophic. The pulmonic semilunar valve had three well-formed cusps (Fig. 8).

On the left side of the heart we saw an enormous atrium, much larger than the right atrium and with a much thicker wall. The septal wall of this left atrium presented the irregular contour of the septum primum as it closes over the foramen ovale. The left-sided atrioventricular valve resembled a tricuspid rather than a mitral valve. It will be described in greater detail. The ventricle on the left side of the heart was greatly hypertrophied and dilated. The septal wall was markedly trabeculated, as is a normal right ventricle. The outflow tract and inflow tract of this ventricle were subdivided by a thick muscular ridge which had the appearance of a crista supraventricularis. Thus, this ventricle morphologically resembled a right ventricle (Fig. 9).

At this point we must consider the terminology relative to naming the cardiac chambers. How shall we label a chamber of the heart, and decide whether it is a right or left chamber? We cannot label it according to the vessels that enter or those that exit. The most reliable criterion is the structure of the septal wall of each chamber.[1] The right atrium is that chamber which on its septal wall has a fossa ovalis and a limbus. The right atrium of this heart was therefore in the normal location. The septal wall of the left atrium has the irregular configuration of the septum primum covering the foramen secundum. This was the situation in this case. The right ventricle is that chamber which has a crista supraventricularis subdividing its outflow and inflow tracts and a trabeculated septum with papillary muscles arising from the septum. That fits the description of the chamber that was on the left side in this case. The right ventricle must therefore be considered to be transposed or inverted. The left ventricle is that chamber which has a relatively smooth septal wall, with no papillary muscles arising from it, and no crista supraventricularis. This was the appearance of the ventricle on the right side of this heart. We cannot name these ventricles merely left or right. In our case we must speak of the *left-sided* ventricle or the *systemic* ventricle or the *morphologic right* ventricle; and again we must speak of the *right-sided* ventricle or the *pulmonary* or *venous* ventricle or the *morphologic left* ventricle. The pulmonary trunk arises from the morphologic left ventricle, and the aorta arises from the morphologic right ventricle, a situation analogous to that

Fig. 8.

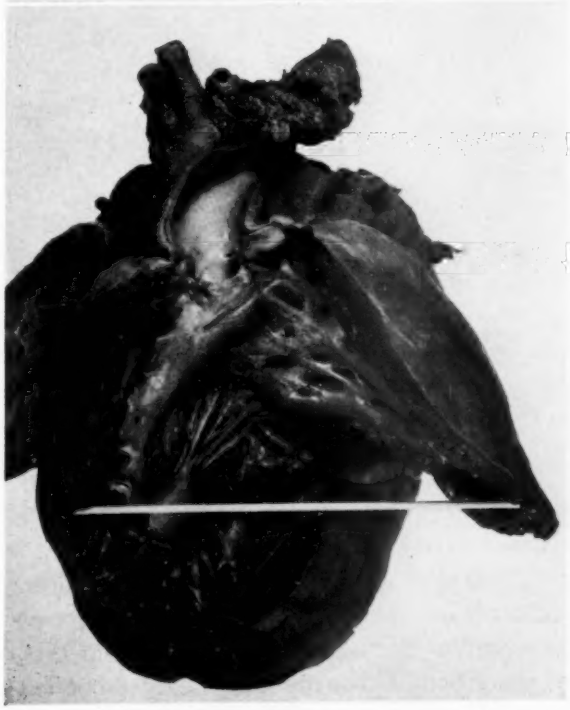

Fig. 9.

Fig. 8.—Opened heart, exposing right-sided (morphologic left) ventricle and pulmonary valve. The septal wall is relatively smooth and no papillary muscles arise from it. No crista supraventricularis is present, the membranous septum is visible, and the atrioventricular valve leaflet is continuous with the semilunar valve.

Fig. 9.—Opened heart, exposing the hypertrophied left-sided (morphologic right) ventricle and aortic valve. A crista supraventricularis and trabeculated septal wall are present. The aortic cusps are fenestrated.

of a complete transposition. As is usually the case in this anomaly, the atrioventricular valves followed the pattern of inversion of the ventricles. To recapitulate, we have a levocardia, because the apex pointed to the left, and we have what Lev[1] refers to as a mixed levocardia, because the right atrium enters into the left ventricle, and the left atrium enters into the right ventricle. We have a transposition of the great vessels which has been termed a corrected transposition because the functional pattern of blood flow through the heart was normal; that is, it was corrected functionally even though the great vessels arose from the morphologically "wrong" ventricles.

Fig. 10.—Opened heart, exposing the left-sided atrioventricular (tricuspid) valve. There are gaps at the commissures and clefts of the leaflets, with chordae tendineae inserted along the thickened valve margins. Chordae to the posterior and septal leaflets arise high on the ventricular wall.

It would be anticipated that corrected transposition by itself, with no associated anomalies, should be compatible with a long life and lead to no cardiac difficulty. In the rare case in which no other anomalies have been present this has apparently been true.[2] However, there are usually associated anomalies. An interventricular septal defect is common; pulmonary stenosis and patent ductus arteriosus also occur.[3] Several cases of corrected transposition with anomalies of the left atrioventricular tricuspid valve associated with clinical mitral insufficiency have been described.[2] Edwards[4] has included corrected transposition with insufficiency of the left atrioventricular valve in his discussion of the differential diagnosis of mitral valvular disease.

In the present case there was a marked deformity of the left atrioventricular tricuspid valve (Fig. 10). In other described cases the deformity was due either to an Ebstein malformation of this valve or to anomalous insertions of the chordae tendineae which appeared to restrain the leaflets from complete closure.[2] In our

case the septal and posterior portions of the valve did have short chordae tendineae which attached high on the ventricular wall and appeared very likely to have contributed to inadequate apposition of the leaflets. In addition, the valve leaflets were deformed. The three tricuspid leaflets appeared to be partially subdivided by clefts. There were wide gaps at the commissures and clefts of the leaflets. Deficiencies in the leaflets have been described in cases of healed bacterial endocarditis,[4] but this does not appear to be the situation in our case: there were no ruptured chordae tendineae, and the deformities of the leaflets were not circumscribed or focally exaggerated at the sites of the valvular deficiencies. The valve leaflets showed a marked irregular thickening along their margins, raising the question of possible old rheumatic valvulitis superimposed on the congenital deformity. Evidence of marked insufficiency of the valve was indicated by the presence of regurgitant pockets in the left atrium. There was marked endocardial thickening in the left atrium. This was especially remarkable over the posterior atrial wall, where it may be interpreted as a "jet" lesion from impingement of the regurgitant blood stream (Fig. 11).

Fig. 11.—Opened heart, exposing the greatly enlarged left atrium and the left-sided atrioventricular valve. A double row of regurgitant endocardial pockets lies above the posterior leaflet, the upper row appearing to face away from the apex of the heart. Higher on the posterior wall is an undermined endocardial thickening representing a "jet" lesion. Part of the coronary venous return emerges through the large opening in the center of this endocardial patch.

An additional anomaly in this case involved the coronary venous system. The greater venous drainage entered the left atrium high in the posterior wall, and the remainder entered at the base of the right auricular appendage (Fig. 12).

Morphologic stigmata of rheumatic fever in inactive cases may be mild and difficult to distinguish from changes due to aging.[5] In our case such changes would also have to be distinguished from hemodynamic changes occurring in a

heart that was anatomically and functionally abnormal. In cases of rheumatic fever there is usually microscopic involvement of most or all of the valves, particularly the valve rings, although the incidence is decreased in inactive cases.[6,7]

Microscopic sections from the thickened left atrioventricular valve showed extensive deposition of collagen and elastic tissue. There was no inflammatory cellular reaction and no vascularization of the valve ring or leaflets. Except for some thickening, the other valves revealed no significant changes. The valve rings were well formed. Endocardial thickening was present in all chambers, and endocardial fibroelastosis was especially marked in the left atrium. Such changes in the valves and endocardium could occur in inactive rheumatic fever; however, the microscopic features do not indicate an inflammatory basis. It seems more likely that these valvular abnormalities were of hemodynamic origin.

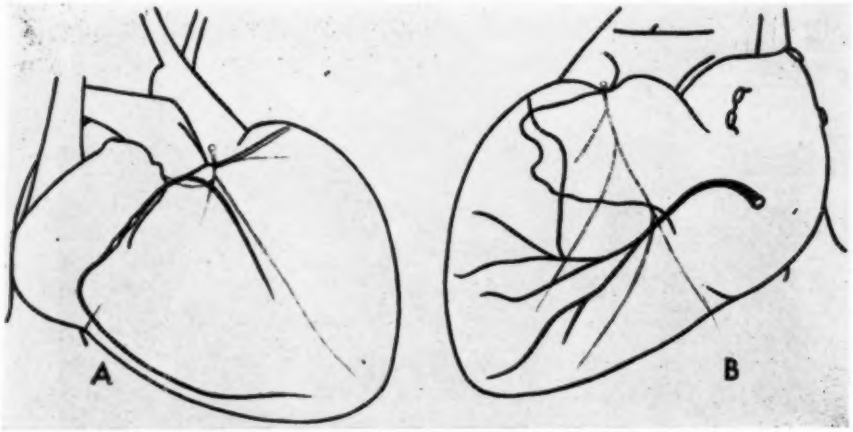

Fig. 12.—Diagram of the heart in situ, showing the anomalous course of the coronary vessels. Gray lines represent coronary arteries; black lines represent coronary veins. *A*, Anterior aspect of heart. *B*, Posterior aspect of heart.

The myocardium of the left atrium showed increased interstitial myocardial fibrosis but no fusiform scars along the vessels suggestive of healed Aschoff bodies. In the systemic ventricular wall there was a mild degree of patchy fibrosis, insufficient to account for primary myocardial failure. There was some interstitial fibrosis in the right atrium. The myocardial fibers of the left atrium and systemic ventricle were markedly hypertrophied. In the pulmonary ventricle the fibers were not enlarged.

Miscroscopically, the epicardium of the left atrium showed hypocellular, dense, fibrous tags of a previous organized epicarditis. The etiology of this feature is obscure. The most that could be found in the way of an inflammatory reaction were a few sparsely scattered lymphocytes and histiocytes in the pericardium and an occasional small lymphocytic focus in the myocardium. These were nonspecific and very mild.

Secondary vascular changes were manifest in the lungs. The muscular pulmonary arteries had thick muscular mediae and scalloped elastic laminae.

Small vessels the size of arterioles or venules showed a striking intimal thickening of variable degree, occasionally with almost complete obliteration of the lumina. In fortuitous sections it was possible to observe small muscular arteries with moderately cellular intimal thickening which continued into nonmuscular arterioles. Finely collagenized intimal thickening which was not clearly demarcated from the media was also demonstrable in venules and small veins. There was a small organizing infarct in the upper lobe of the right lung.

Pathologic Diagnoses.—Corrected transposition of the great vessels with insufficiency of left-sided atrioventricular (tricuspid) valve: mixed levocardia, atria normal, ventricles inverted, corrected complete transposition of the arterial trunks. Congenital deformity of the left atrioventricular (tricuspid) valve with insufficiency and hemodynamic changes; left atrial and systemic (morphologic right) ventricular dilatation and hypertrophy, marked; right atrial and pulmonary (morphologic left) ventricular dilatation and hypertrophy, moderate; endocardial fibrosis of left atrium, hemodynamic, marked; endocardial fibrosis of right atrium and both ventricles, mild to moderate; fibrosis of myocardium of left atrium, moderate, and systemic ventricle, mild; old organized epicarditis of left atrium (etiology undetermined); hydropericardium. Aberrant coronary venous drainage.

Chronic passive hyperemia of lungs; medial hypertrophy of muscular pulmonary arteries; hyperplastic intimal sclerosis of pulmonary arterioles and venules; solitary organizing infarct of lung with focal fibrinous pleuritis. Chronic passive hyperemia of liver. Periprostatic phlebothrombosis. Acute passive hyperemia of viscera. Multiple congenital accessory spleens. Mesenteric nodule of heterotopic pancreatic ducts.

Diagnosis: Mixed Levocardia With Corrected Transposition and Insufficiency of the Left-Sided A-V Valve

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Annotations

Cardiac Bypass Without an Artificial Lung

Following the development of pump oxygenators, intracardiac surgery has become accepted practice. In a field so young, it is not surprising that techniques and apparatus do not conform to a set pattern. Many of the pioneers of cardiac surgery designed their own apparatus for cardiopulmonary bypass. The disk, the membrane, and the bubble oxygenator have emerged from leading centers.

Less has been written on the simpler, and perhaps more physiologic, plan of bypassing the heart without bypassing the lungs.[1] For the successful repair of complex abnormalities of the heart, the intracardiac field must be dry, or nearly so, and the rest of the body must be adequately perfused. There is no necessity to bypass the lungs, although the vast majority of workers have found it convenient to do so, and to employ a heart-lung machine to perfuse the rest of the body. On theoretical grounds it would be equally satisfactory to divert blood from the heart but to permit circulation through the pulmonary vascular bed. A mechanical device would be required to take over the function of the heart, but there would be no need for an artificial oxygenator. The assumption that the subject's own lungs would function better than an artificial oxygenator is a reasonable one, and the problem has been to allow them to do so during the conditions of total cardiac bypass without producing congestion, edema, or infarction consequent to supplying more blood to the pulmonary arterial bed than can be drained from the pulmonary venous bed.

Two chief causes of failure in the early attempts at cardiac bypass with autogenous oxygenation were the use of but limited portions of the pulmonary vascular bed, and failure to provide adequate substitution for the bypassed right ventricle. Blanco and Bailey[2] in their early attempts employed an isolated autogenous lobe for gaseous exchange. When this failed, they employed a single lung, and only when this too failed, were both lungs employed. Both Helmsworth[3] and Drew[4] and their associates in their early work relied upon purely passive bypass of the right heart. Both these investigators drained the left atrium and pumped the effluent to the femoral artery. Helmsworth placed a "Y" cannula system with its limbs in the venae cavae and its stem in the pulmonary artery. Drew used no cannulae on the right side, arrested the heart, and hoped that blood would flow passively through the nonfunctioning right atrium and ventricle. Neither author placed an artificial pump between the venae cavae and the pulmonary artery, but relied upon the venous pressure, aided by the respiratory pump, to provide a sufficient head of pressure to perfuse the pulmonary vascular bed so that oxygenated blood would return to the left atrium and thence to the cannula and reservoir, where the circuit would begin again. Ingenious though this method was, it resulted in high mortality in experimental animals, chiefly because of damage to the lungs and to the sequelae of hypervolemia.

Several authors have arrived independently and almost simultaneously at the conclusion that it is necessary to take over by mechanical means the functions of both the left and right ventricles. The left atrium is drained into an open dependent reservoir from which blood is pumped into the femoral artery. A second open dependent reservoir receives the drainage of the venae cavae and coronary sinus (or of the right atrium), and a second pump forces its content into the pulmonary artery. Among the important advantages of the two reservoirs is the fact that the

two pumps do not have to be delicately balanced so that they pump precisely at the same rate throughout the perfusion. Discrepancies between the pumping rate on the two sides are rapidly apparent because the levels of blood in the two reservoirs will then change in opposite directions. Either pump can readily be adjusted to reverse this trend and to restore the reservoirs to their original levels. The studies of Helmsworth indicate that high flow rates can be achieved, and that for periods of one-half hour, normal arterial blood pressure and pH may be maintained.

Bailey and Blanco[5] have used autogenous oxygenation in patients undergoing operations for aortic stenosis and incompetence. More recently, they have added direct perfusion of the coronary arteries and have been able successfully to operate upon the aortic valve for periods considerably longer than 1 hour. Drew[6] and Shields[7] have reported upon a new application for cardiac bypass with autogenous oxygenation. By incorporating a heat-exchange unit into the system they have been able rapidly to induce profound hypothermia. The occurrence of arrhythmias during cooling is not an important problem when apparatus for perfusion is functioning. In their animals, pharyngeal temperatures of 10°C. were employed, and the corresponding temperatures in the mediastinum and rectum were in the vicinity of 8 and 14°C. Perfusion is begun and cooling is continued until cardiac standstill has occurred and the desired temperatures are registered. The pumps are then shut off, and the right and left atrial drains are left open until the heart is drained of blood. After 30 minutes the perfusion is restarted and rewarming is begun. Drew[6] now reports 5 of 7 successfully treated clinical cases.

It is as yet too soon to predict whether autogenous oxygenation will eventually displace conventional oxygenators. The cannulations are more complex, although during the intracardiac manipulations, cannulae may be removed and can be replaced for rewarming. Profound hypothermia will raise its own problems, and a trustworthy technique for its regulation will be needed.

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Systolic Murmurs

Leatham[1,2] showed that systolic murmurs may be of two types. Ejection murmurs arise at the pulmonary or aortic valves when either forward flow is increased or the valve is narrowed. Regurgitant murmurs are due to backward flow of blood through incompetent mitral or tricuspid valves, or to left-to-right shunts through a ventricular spetal defect or aortopulmonary communication. These murmurs may often be distinguished by their timing, character, site, conduction, and associated features; but the distinction is not always easy and may be impossible even with the help of the phonocardiogram.

The transitory fluctuations in central blood flow brought about by deep inspiration or the Valsalva maneuver are widely used to improve recognition of these murmurs. Vogelpoel and his colleagues[3] have recently shown how the inhalation of amyl nitrite may be used in the same way.

The effect of this drug on the circulation has two phases. There is widespread systemic vasodilatation, which probably affects the small veins more than the arterioles.[4] This causes pooling of blood in the venous reservoir and a fall in venous return and in cardiac output. This, together with arteriolar dilatation, results in a fall of systemic arterial pressure; tachycardia follows through the baroceptor mechanism. At the same time there is an increased sympathetic discharge which, as the effect of amyl nitrite passes off, constricts the systemic arterioles and venules. There follows an increase in venous return and cardiac output; the systemic arterial pressure rises and frequently "overshoots." The first phase of hypotension and diminished output lasts about 20 seconds; the second phase is complete in about 1 minute.

Vogelpoel and co-workers found that the regurgitant systolic murmurs of ventricular septal defect, patent ductus, and mitral incompetence become softer during the first phase and related this to the diminished resistance to forward flow. The murmurs regain their original loudness after 45 seconds and may become even louder if the arterial pressure "overshoots." The murmur of tricuspid incompetence does not diminish during the first phase but increases greatly during the second phase, when flow through the right heart is augmented. Ejection murmurs, except in the tetralogy of Fallot, become louder during the second phase, as would be expected from the increased flow. In the tetralogy of Fallot, on the other hand, the pulmonary systolic murmur diminishes in the first phase, presumably because of preferential flow through the septal defect.

Combined lesions and the presence of cardiac failure modify these responses in various ways, and diastolic murmurs are influenced in fairly characteristic fashion. This simple, safe, and repeatable bedside test may prove to be a most useful addition to diagnostic resources.

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Molar Sodium Lactate Antagonism of Myocardial Depressants

Potassium, quinidine, and procaine amide in excessive amounts produce severe myocardial depression. The cardiotoxic effects of these agents include depression of the sinoatrial pacemaker, disturbances of atrioventricular and intraventricular conduction, and ventricular arrhythmias with death following ventricular fibrillation or cardiac arrest.[1-3] Excretion and/or metabolism of these agents may be delayed, particularly in the presence of congestive heart failure,[3-5] whereas their cardiotoxic effects may require immediate treatment.

Molar sodium lactate has been found to be effective in the treatment of cardiac disturbances associated with hyperkalemia.[6] Similarity of the electrocardiographic abnormalities in cases of hyperpotassemia and cases of quinidine and procaine-amide intoxication led to the investigation of the effectiveness of molar sodium lactate in the therapy of the cardiotoxic effects of these drugs.[7] Experimental studies in animals demonstrated reversal by molar sodium lactate of both the hypotension and electrocardiographic changes (arrhythmias, QRS widening) produced by toxic doses of quinidine and procaine amide.[7-9] These experimental findings have been confirmed,[10,11] and molar sodium lactate has been employed successfully by several groups in the treatment of quinidine and procaine-amide poisoning in human beings.[8,12,13]

Molar sodium lactate is administered intravenously, and the dosage varies depending on the patient's response as evidenced by changes in the electrocardiogram and blood pressure. The preferred dosage has been 40 ml. over a 3-minute interval, repeated every 20 to 30 minutes to a total of 120 to 200 ml.,[12,13] although as much as 250 ml. of a continuous infusion have been given in 30 minutes.[12] Since molar sodium lactate—particularly in the presence of congestive heart failure—

may precipitate pulmonary edema, patients treated with the drug should be examined frequently for evidence of increased pulmonary congestion. Administration of intravenous molar sodium lactate should be made in conjunction with continuous electrocardiographic observation, and the infusion should be discontinued if ventricular premature contractions become more frequent or runs of ventricular tachycardia, which were previously absent, appear under influence of the drug.

The immediate beneficial effects of molar sodium lactate in cases of quinidine and procaine-amide intoxication include a rise in blood pressure and reversal of the electrocardiographic abnormalities, with abolition of arrhythmias and conduction disturbances.[7-13] These changes are associated with lowering of the levels of plasma potassium, quinidine, or procaine amide.[7-13]

Present evidence appears to indicate that quinidine and procaine amide produce their pharmacologic effects by interfering with the movement of sodium and potassium ions across the myocardial cell membrane.[14,15] Antagonism by molar sodium lactate to these cardiotoxic agents is felt to be due to the creation of an ionic gradient of sodium and potassium opposing the effect of quinidine and procaine amide.[8,9,13]

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Acute Nonspecific Pericarditis (Idiopathic Pericarditis, "Virus" Pericarditis, Acute Benign Pericarditis)

The diagnosis of acute pericarditis of unknown etiology has been made with increasing frequency during the last two decades, and, in fact, is the most common type of pericarditis encountered in the Cincinnati area.[1] This variety of pericarditis is characterized by fever (99°-105° F.), and sudden precordial pain which often radiates to the neck, shoulders, and upper extremities.

The pain is usually intensified by deep breathing, coughing, and rotation of the trunk. Occasionally, the pain may be limited to the epigastrium. Dyspnea, cough, malaise, nausea, and vomiting may be present. A pericardial friction rub is heard in 70 per cent of the cases, and often appears within hours of the onset of pain. The duration of the rub is highly variable, and may occasionally persist for weeks. Moderate enlargement of the cardiopericardial silhouette usually develops. This is best demonstrated by serial roentgenograms and is probably due to pericardial effusion rather than cardiac dilatation. Frequently, small evanescent patches of pneumonitis and pleuritis develop. Characteristic electrocardiographic evidence of pericarditis appears promptly, with elevation of S-T segments in the standard and in the majority of the precordial leads. Usually within a week the S-T segments return to the base line, and the T waves flatten or become inverted.

The initial illness usually lasts several weeks but may persist for months. Unfortunately, frequent and repeated recurrences are common but generally are less severe and of shorter duration than the initial illness. Complete recovery almost invariably occurs, although 5 cases with fatal tamponade have been reported. One of these had a hemorrhagic effusion, which was probably caused by the administration of anticoagulants due to a mistake in diagnosis. Chronic constrictive pericarditis rarely if ever develops as a complication of acute nonspecific pericarditis.

The pericardial fluid may be straw-colored or bloody, without characteristic cytology, and when cultured for bacteria, is sterile.

Fever, rather frequent antecedent upper respiratory infections, leukocytosis, and increased sedimentation rate strongly suggest an infectious etiology. No consistent elevation of antistreptolysin titers has been noted. Sera from children with this form of pericarditis have been negative for cold agglutinins, for influenza viruses, for lymphogranuloma venereum, psittacosis, and Q fever. Kagan and Bernkopf[2] have reported the isolation of Coxsackie virus, Group B, Type 3, from the pericardial fluid of a 10-month-old girl. Gillett,[3] in a review of the literature concerning Coxsackie viruses and pericarditis, has reported, in 19 cases, the isolation of Coxsackie viruses from the stools, or serologic evidence of infection with these viruses. The 4 cases personally observed by Gillett were encountered during an epidemic of pleurodynia. Gillett concluded that the "Coxsackie viruses may well be a major cause of the syndrome of acute benign pericarditis." Further studies may be helpful in indicating whether Coxsackie virus infection is merely coincidental or actually an etiological agent of nonspecific pericarditis. It should be mentioned that in a number of characteristic cases of nonspecific pericarditis there has been no serologic evidence of Coxsackie virus infection.

Since there is an intimate clinical common denominator which characterizes acute nonspecific pericarditis, the postcardiotomy or postmitral commissurotomy syndrome, and the postmyocardial infarction syndrome of Dressler, the etiology of nonspecific pericarditis is further complicated. Several hypotheses have been suggested: these include the activation of a latent virus by nonspecific injury to the myocardium, a hypersensitivity reaction from antigens, such as blood in the pericardial cavity, or antigenic products created by myocardial necrosis. Careful studies to exclude or implicate Coxsackie viruses in postcardiotomy and postmyocardial infarction pericarditis would be desirable.

Unquestionably there have been many cases erroneously diagnosed as myocardial infarction which actually were instances of acute nonspecific pericarditis, since the clinical pictures and, occasionally, the electrocardiographic abnormalities may be difficult to differentiate. However, marked elevation of serum glutamic-oxalacetic transaminase, so characteristic of myocardial infarction, does not occur with pericarditis, although moderate rises in this enzyme in a few cases of nonspecific pericarditis have been reported. Tuberculous and rheumatic pericarditis, as well as the pericarditis associated with disseminated lupus erythematosus, may also closely simulate nonspecific pericarditis. Because the specific chemotherapeutic treatment for tuberculous pericarditis is usually lifesaving, the precise differentiation is of great practical importance. A negative tuberculin skin test is helpful in excluding a tuberculous etiology. Occasionally, pericardial biopsy, a rather formidable surgical procedure, has been performed in cases in which clinical study and examination of the pericardial fluid for acid-fast organisms have failed to establish a definite diagnosis. However, culture and histologic examination of the pericardium have not infrequently been disappointing, showing only nonspecific inflammation and, consequently, not establishing a diagnosis of the etiology.

There is no specific treatment for acute nonspecific pericarditis. Antibiotics are useless, and the value of steroid therapy controversial. Salicylates promote comfort and should be supplemented with Demerol or codeine during the period of intense pain. Recently, in 3 patients with persistent, intractable and incapacitating pain, pericardiectomy which effected a cure has been reported.[4]

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Acute Anoxic Cardiac Failure in Pulmonary Heart Disease

There is increasing awareness that chronic lung disease may lead ultimately to cardiac disorder. Recent reports[1,2] indicate that in Britain, pulmonary heart disease is responsible for congestive cardiac failure in 15 to 35 per cent of the cases, whereas in such geographically diverse cities as Belgrade[3] and Auckland[4] the incidence approximates 15 per cent. Despite this, interest in pulmonary heart disease has been slow to develop. As a link between respiratory and cardiac disease, research in this field tends to fall between two schools, since it is wholly the province of neither speciality. Moreover, it is not always generally appreciated that pulmonary heart disease may present in different phases of the disorder, e.g., without cardiac failure, with chronic cardiac failure, or with acute anoxic cardiac failure. The term "cor pulmonale," although widely used, fails to take this into account; consequently, its use is often indefinite and associated with confused clinical concepts. Frequently also in acute anoxic failure, signs of respiratory infection may be dominant and cardiac failure may pass unnoticed, so that the true incidence is underestimated. Even when considered, the certain diagnosis of pulmonary heart disease may prove elusive, since clinical, radiologic, and electrocardiographic assessment fail to establish the presence of right ventricular hypertrophy in about one third of the cases.

Critical evaluation of relevant physiology does much to elucidate the various phases of pulmonary heart disease and to emphasize the importance of anoxia in cardiac failure. In chronic lung disease, reductions in diffusion capacity, alveolar ventilation, and, to a lesser extent, pulmonary vascular bed result in varying degrees of anoxia and carbon-dioxide retention. Often, the central stimulant action of carbon dioxide ultimately becomes impaired and leaves anoxia as the sole significant physiologic stimulant of the respiratory center. It is now well recognized that relief of anoxia under these circumstances may lead to apnea and carbon-dioxide narcosis.[5] In addition to changes in blood gases, pulmonary heart disease is associated with some element of pulmonary hypertension: due predominantly, in part, to reduction of pulmonary vascular cross-sectional area and loss of lung compliance, and, in part, to anoxia which produces active pulmonary vasoconstriction.[6] A balance is generally attained when reasonable function is preserved despite these changes. When anoxia is insufficient to provoke hyperkinetic circulatory states, relatively low cardiac outputs often result. A fresh respiratory infection under these conditions disturbs the equilibrium and may precipitate severe anoxia. Levels of arterial oxygen saturation of 50 to 75 per cent are not uncommon. Subsequent peripheral vasodilatation and the development of a hyperkinetic circulatory state produce the features usually ascribed to "cor pulmonale." Further retention of carbon dioxide and changes in blood pH cause drowsiness, confusion, and even coma. Pulmonary vasoconstriction increases and, together with additional anoxic impairment of cardiac muscle action, leads to right ventricular dilatation and subsequent cardiac failure. With persistent

anoxia this becomes progressive, and further complications of ventricular fibrillation, renal failure and anuria,[7] hepatic failure,[8] cerebral damage,[9] and adrenal apoplexy[2] are described. Logically, this can only be countered by relief of anoxia. The essential problem lies in maintaining sufficient depth and frequency of respiration to avoid carbon-dioxide narcosis while oxygen is administered and while antibiotics help overcome infection.

For therapeutic relief of anoxia it appears necessary for oxygen to be administered continuously.[2] This may be accomplished by mechanical respirator[10] or by oxygen tent with chemical stimulation of the respiratory center,[11,12] when necessary. Whereas the former method is obviously ideal in controlling retention of carbon dioxide, it is impractical where the requisite expensive equipment and adequate specialized staff are not available. Before treatment, some assessment of the need for respiratory stimulation may be obtained from estimations of arterial oxygen, carbon dioxide, and pH. In less severely affected patients, stimulation may prove unnecessary, but it is frequently essential in patients in whom the disturbance is more severe, and particularly in those in whom right ventricular strain is evident electrocardiographically. Under the latter circumstances it has been shown[2] that through the frequent use of intramuscular injections of nikethamide for respiratory stimulation, patients can be treated in oxygen tents with considerably improved prognosis and without deaths attributable to carbon-dioxide narcosis. When there is danger of narcosis developing despite intramuscular nikethamide, additional intravenous doses are advocated. Severely affected patients should be given respiratory stimulants before clinical evidence of narcosis develops, and oxygen therapy should be continued until arterial oxygen saturation remains over 90 per cent without assistance. Respiratory stimulants are frequently unnecessary after 4 or 5 days, but oxygen therapy may be required for 2 weeks or longer. When levels of arterial oxygen remain below 90 per cent after prolonged treatment, chronic cardiac failure tends to develop without exacerbations of respiratory infection, and it is possible that this is an indication for long-term, intermittent oxygen therapy.[4] The principal disadvantage of nikethamide lies in its relatively short action; however, other respiratory stimulants have proved disappointing and the introduction of a suitable effective, long-acting substitute is overdue.

It was noted in the same paper[2] that brisk spontaneous diuresis occurred in the absence of digitalis or diuretic treatment within a few days of elevation of arterial oxygen saturation to 90 per cent or more. In the interval between attainment of these levels and diuresis, oliguria persisted, the hyperkinetic circulatory state gradually diminished, and clinical edema increased. Simpson[8] suggests that the renal lesion is a functional one, secondary to anoxia; however, it is known that in the presence of severe anoxia, definite tubular damage may occur.[3,7] Further observations on renal function in anoxic failure have revealed that spontaneous diuresis may be deliberately interrupted by permitting anoxia to recur, and initiated again by restoration of adequate levels of oxygen in the blood.[4] It would appear that relief of anoxia, by permitting improved renal and cardiac function, is fundamental in contemplating diuretic therapy. The value of diuretic agents in the treatment of anoxic failure requires more detailed assessment in this light.

Further problems await elucidation. The influence of prompt and adequate relief of anoxia on the long-term prognosis remains to be determined. Fulton[13] found that once cardiac failure developed in patients with pulmonary heart disease, death ensued in all cases within 2 years. Preliminary results[4] suggest that early restoration of adequate levels of oxygen is associated with a 2-year survival rate of approximately 50 per cent. Further investigation is necessary, however, in order to determine the levels of oxygen that must be maintained in order to avoid continued cardiac deterioration, and the effects which close surveillance and intelligent use of antibiotics may have on prolongation of life. Further investigation also is necessary to determine the exact nature of "carbon-dioxide narcosis." Frequently there is no close correlation between arterial carbon-dioxide content or tension and the degree of narcosis. Whereas the accumulation of carbon dioxide plays a substantial part in the development of neurological disturbance, it is possible that changes in blood pH and electrolytes may contribute significantly. The results of further research in the field of pulmonary heart disease are awaited with considerable interest in many parts of the world.

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Book Review

CARDIAC AUSCULTATION. By J. Scott Butterworth, M.D., Associate Professor of Medicine New York University Postgraduate Medical School; Maurice R. Chassin, M.D., Associate Professor of Clinical Medicine, New York University Postgraduate Medical School; Robert McGrath, M.D., Associate Professor of Clinical Medicine, New York University Postgraduate Medical School; and Edmund H. Reppert, M.D., Assistant Professor of Clinical Medicine, New York University Postgraduate Medical School. Second revised and enlarged edition, New York, 1960, Grune & Stratton, Inc., 102 pages. Price $6.25.

Within the limits of its directed purpose, this little book represents a remarkable distillation of accumulated information relating to clinical cardiovascular auscultation. It is ideally suited for the busy general practitioner who wishes to keep abreast of developments in this field without the burdens of the complex or controversial. References are few. Simplicity and practicality are its keynotes. It is recommended reading for its intended audience.

Announcements

The Vermont Heart Association, in cooperation with the University of Vermont College of Medicine, will sponsor a SEMINAR ON ATRIAL ARRHYTHMIAS.

The Seminar will be held in Burlington, Vt., on Sept. 17 and 18, 1960. Among the guest speakers who plan to participate are Dr. S. Bellet, Dr. B. F. Hoffman, Dr. W. C. Holland, Dr. H. D. Levine, and Dr. D. Scherf.

Further information can be obtained from: Eugene Lepeschkin, M.D., Professor of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vt.

THE AMERICAN UROLOGICAL ASSOCIATION offers an annual award of $1,000 (first prize of $500, second prize of $300, and third prize of $200) for essays on the result of some clinical or laboratory research in the field of urology. Competition is limited to urologists who have been graduated not more than ten years, and to hospital internes and residents doing research work in urology.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Biltmore, Los Angeles, Calif., May 22-25, 1961.

For full particulars write the Executive Secretary, William P. Didusch, 1120 North Charles St., Baltimore, Md. Essays must be in his hands before Dec. 1, 1960.